SYNTHESIS OF CERTAIN SCHIFF BASES OF 3-FORMYL-2-QUINOLONES AND EVALUATION OF THEIR ANTIMICROBIAL AND ANTIMYCOBACTERIAL ACTIVITIES

A Dissertation submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
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MASTER OF PHARMACY
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Submitted by
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COIMBATORE – 641044

OCTOBER 2017

CERTIFICATE

This is to certify that the M.Pharm dissertation entitled, **"Synthesis of certain Schiff bases of 3-formyl-2-quinolones and evaluation of their antimicrobial and antimycobacterial activities"** being submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai was carried out by **Mr.Prabhakar.K (Reg.No.261515104)** in the Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under my direct supervision and guidance to my fullest satisfaction.

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Date:

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This is to certify that the Antimicrobial studies which was part of the dissertation entitled, **"Synthesis of certain Schiff bases of 3-formyl-2-quinolones and evaluation of their antimicrobial and antimycobacterial activities"** was carried out by **Mr.Prabhakar.K (Reg.No.261515104)** in the Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Dr. R. Vijayaraj M.Pharm., Ph.D.,** Professor, Department of Pharmaceutical Chemistry, College of Pharmacy, SRIPMS, Coimbatore.

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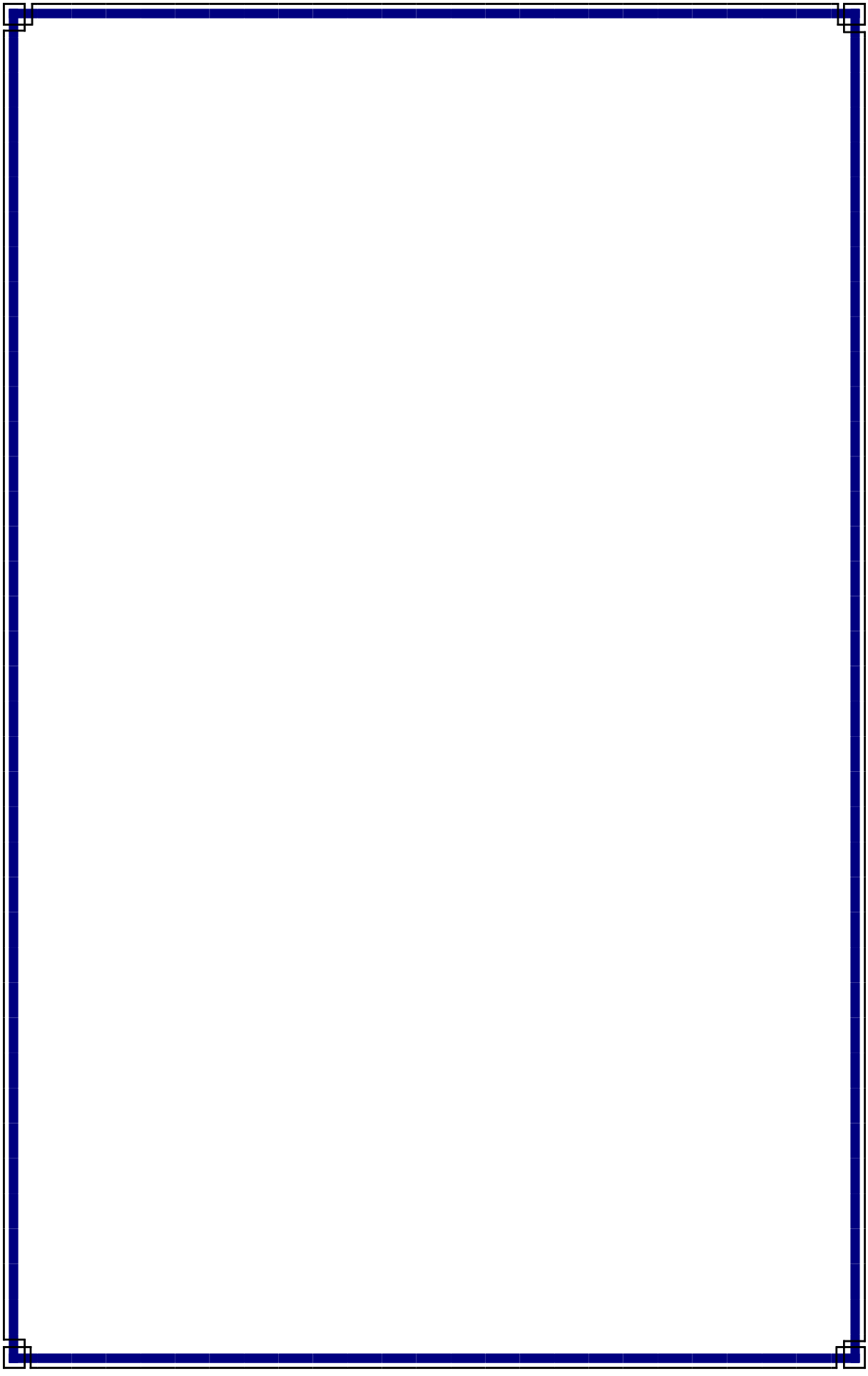

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CONTENTS

INTRODUCTION

Antimicrobial drugs have caused a dramatic change not only of the treatment of infectious diseases but of a fate of mankind. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in reality, emerging and re-emerging infectious diseases have left us facing a countercharge from infections. Infections with drug resistant organisms remain an important problem in clinical practice that is difficult to solve. If an improper antimicrobial agent happens to be chosen for the treatment of infection with drug-resistant microorganisms, the therapy may not achieve beneficial effect, and moreover, may lead to a worse prognosis. In addition, in a situation where multidrug-resistant organisms have spread widely, there may be quite a limited choice of agents for antimicrobial therapy. At present, fewer brand new antimicrobial agents are coming onto the market. Considering this situation together with the increasing awareness of drug safety, we are now facing a situation of severely limited options among antimicrobial agents.

The history of antimicrobial agents, and thereafter describes resistant organisms that have emerged in response to antimicrobial agents and discusses practical clues to prevent resistant microorganisms.

HISTORY OF THE DEVELOPMENT OF ANTIMICROBIAL AGENTS

Looking back on the history of human diseases, infectious diseases have accounted for a very large proportion of diseases as a whole. It was not until the latter half of the 19th century that microorganisms were found to be responsible for a variety of infectious diseases that had been plaguing humanity from ancient days. Accordingly, chemotherapy aimed at the causative organisms was developed as the main therapeutic strategy.

The first antimicrobial agent in the world was salvarsan, a remedy for syphilis that was synthesized by Ehrlich in 1910. In 1935, sulfonamides were developed by Domagk and other researchers. These drugs were synthetic compounds and had limitations in terms of safety and efficacy. In 1928, Fleming discovered penicillin. He found that the growth of Staphylococcus aureus was inhibited in a zone surrounding a contaminated blue mold (a fungus from the Penicillium genus) in culture dishes, leading to the finding that a microorganism would produce substances that could inhibit the growth of other microorganisms. The antibiotic was named penicillin, and it came into clinical use in the 1940s. Penicillin, which is an outstanding agent in terms of safety and efficacy, led in the era of antimicrobial chemotherapy by saving the lives of many wounded soldiers during World War II.

During the subsequent two decades, new classes of antimicrobial agents were developed one after another, leading to a golden age of antimicrobial chemotherapy. In 1944, streptomycin, an aminoglycoside antibiotic, was obtained from the soil bacterium Streptomyces griseus. Thereafter, chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g., vancomycin) were discovered from soil bacteria. The synthesized antimicrobial agent nalidixic acid, a quinolone antimicrobial drug, was obtained in 1962. Improvements in each class of antimicrobial agents continued to achieve a broader antimicrobial spectrum and higher antimicrobial activity.β - lactam antibiotics will be described as an example.

The β-lactam antibiotics include penicillins,cephems, carbapenems, and monobactams. Penicillins were originally effective for Grampositive organisms such as S. aureus. Later, to address penicillin-resistant S. aureus which produces the penicillin-hydrolysing enzyme penicillinase, methicillin was developed. On the other hand, attempts to expand the antimicrobial spectrum yielded ampicillin, which is also effective for Gram-negative Enterobacteriaceae, and piperacillin, which is effective even for Pseudomonas aeruginosa.

Cephems were developed in the 1960s, and came into widespread use. Cephems are classified into several generations according to their antimicrobial spectra.

First-generation cephems (cefazolin, etc.) are effective only for Gram-positive organisms and Escherichia coli, although their antimicrobial activity against these organisms is potent.

Second-generation cephems (cefotiam, etc.) have an extended antimicrobial spectrum that covers not only Gram-positive but also Gramnegative organisms including other Enterobacteriaceae.

Third-generation cephems (ceftazidime, cefotaxime, etc.) have higher efficacy for Gramnegative organisms, and some drugs of this generation are also effective for P. aeruginosa, although the antimicrobial activity against Grampositive organisms is generally lower than that of the first generation. Carbapenem is an antibiotic class including panipenem, imipenem and meropenem. These drugs are effective not only for Gram-positive and Gram-negative bacteria but also anaerobes, and their antimicrobial activity is strong.

The monobactam antibiotic aztreonam exerts an antimicrobial effect only on Gram-negative bacteria. Continuing improvements have been made for antimicrobial agents in various aspects in addition to the antimicrobial spectrum and activity. The drugs have been developed to achieve better pharmacodynamics including the absorption of oral drugs, concentration in the blood, and distribution to the inflammatory focus. In addition, as antimicrobial chemotherapy has been established and matured, more importance has been attached to the drug safety. Antimicrobial agents that are associated with serious side effects have been replaced by other safer drugs.

[82] Quinolone antimicrobials represent an example of drugs with improved pharmacodynamics and safety. Nalidixic acid, the first drug of this class, was active only against Gram-negative bacteria, and its use was limited to urinary tract infections because it achieves only low blood concentrations and poor tissue distribution, and was metabolized rapidly in the human body. In contrast, norfloxacin, which came to market in 1984, maintains a stable metabolic state and exhibits good tissue distribution. Its antimicrobial spectrum is extensive, covering both Grampositive and Gram-negative bacteria including *P. aeruginosa.*

Quinolone antimicrobials developed after norfloxacin have been called new quinolones, and they have still been key drugs. Levofloxacin is the S-(+) enantiomer of the new quinolone ofloxacin. This enantiomer has higher antimicrobial activity than that of the other R-(-) enantiomer of ofloxacin, and is associated with weaker side effects on the central nervous system, such as restlessness and vertigo. Although a large number of companies in various countries have competed in the development of newer antimicrobial agents, the number of brand new drugs has been remarkably decreasing in recent years, with few antimicrobial agents of new classes becoming available. In contrast, infectious diseases continue to attack human beings as emerging and re-emerging infectious diseases, opportunistic infectious diseases, and infection with drug-resistant microorganisms that will be discussed in the next section. Effective utilization of the current limited options is much more important under the dearth of new drugs on the market.

The capacity of microorganisms to acquire resistance to antimicrobial agents has surpassed our imagination. In some cases, antimicrobial agents formerly effective are no longer useful. The history of resistant bacteria will be outlined below.

S. aureus is the resistant bacterium most familiar in the clinical setting. This bacterium rapidly acquired resistance to sulfonamides when they were in use.

Penicillin was initially effective to this microorganism, but resistant strains that produce penicillinase increased in the 1950s.

Therefore, penicillinase-stable methicillin was developed in 1960, as mentioned previously.

However, as early as the following year, 1961, methicillin-resistant *S. aureus* (MRSA) was isolated in the UK.3 Since around 1990, nosocomial infection with MRSA became a social problem. During this period, the target of new antimicrobial agents including second- and third-generation cephems, shifted from Gram-positive to Gram-negative bacteria, and agents with wide spectra but weaker activity against Gram-positive bacteria were widely used.

MRSA acquires resistance to mostlactam antibiotics through its acquisition of the penicillin-binding protein (PBP) 2' gene; PBP2' is an enzyme involved in cell wall synthesis that has low binding affinity for β-lactam antibiotics. In genetic lineage analysis of nosocomial MRSA strains, major nosocomial clones throughout the world would converge on only seven types.4 On the other hand, community associated methicillin-resistant *S. aureus* (CAMRSA), which was noticed in the US around 1997, is of a different type from nosocomial MRSA.

Fortunately, MRSA so far in Japan have responded to glycopeptide antibiotics such as vancomycin. However, in the latter half of the 1990s, vancomycin-intermediate *S. aureus* (VISA) was reported in this country. It is thought that thickening of the cell wall contributes to decreased sensitivity to this drug. On the other hand, vancomycin-resistant *S. aureus* (VRSA) reported in the US seemed to acquire the resistance genes horizontally from vancomycin-resistant enterococci (VRE).5 In Japan, there have been no reports of VRSA strains so far, partially at least, due to lower detection rates of VRE than those in Western countries. Although *S. pneumoniae* was originally susceptible to penicillin,

penicillin-intermediate *S. pneumoniae* (PRSP) strains were found in the latter half of the 1960s, and penicillin-resistant *S. pneumoniae* (PRSP) strains in the latter half of the 1970s.

In Japan, PRSP was found in the 1980s, and the detection of PRSP strains began to increase around 1990.

Frequent use of oral cephem antibiotics seems to be responsible for this increase in PRSP. There has also been a remarkable increase in macrolide resistance in this species, which seems also due to the frequent use of macrolides in this country. Ampicillin was initially effective for Haemophilus influenzae.

However, in the 1980s, some of this species were found to produce β -lactamase, thereby becoming resistant to ampicillin. In 1990s, such _-lactamase-producing strains decreased in Japan, however, strains that acquired highly resistance β -lactam through mutations in PBP genes, increased instead. These are called as β-lactamase-negative ampicillin-resistant (BLNAR) strains, and they are more common in Japan than in other Western countries. It has been speculated that increased use of oral cephem antibiotics is also responsible, similar to the situation with PRSP.

Although *P. aeruginosa* are intrinsically resistant to many antimicrobial agents, the emergence of *P. aeruginosa* strains resistant to all of three classes of antimicrobials, i.e., carbapenems, quinolones, and aminoglycosides is a recent concern. These multidrug resistant *P. aeruginosa* (MDRP) sometimes seems to cause an outbreak in some institutions. MDRP has complex mechanisms of drug resistance, including reduced membrane permeability due to decreased outer membrane protein (D2 porin), overexpression of efflux pump, mutation of the quinolone target (DNA gyrase), production of aminoglycoside modification enzyme, and production of metallo-β- lactamase (carbapenem-hydrolysing enzyme).

Some resistance genes are horizontally transferred by conjugative plasmids. Gonococci used to be susceptible to penicillin and quinolone, but currently they are resistant to both agents in Japan. In particular, quinolone had been the first-choice drug for gonococcal infection in the 1980s because of the potential advantage in the case of co-infection with Chlamydophila. However, since almost all the strains have become resistant to quinolones, the 1999 guidelines declared against the use of quinolone for gonococcal infection.

There are major options exist for the control of bacterial diseases:

1) Disrupt or halt transfer of bacteria from person to person and from the environment to people
2) Treat cases of disease with antibiotics
3) Prevent disease through vaccination or

There are different mechanisms to inhibit the micro organisms growth.

INHIBITORS OF BACTERIAL CELL WALL SYNTHESIS

Penicillins

Cephalosporins

Vancomycin

INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

Aminoglycosides

Linazolid

Tetracycline

Chloramphenicol

Erythromycin

Clindamycin

INHIBITION OF NUCLEIC ACID SYNTHESIS AND FUNCTION

Rifampacin

Fluoroquinolones

Antimetabolites

Sulfonamides

AGENTS AFFECTING MEMBRANE PERMEABILITY

Polymyxin B

Amphotericin B (Anti fugal)

GENETIC STRATEGIES FOR ANTIBACTERIAL DRUG DISCOVERY

This approach provides an advantage compared with classical antimicrobial-discovery approaches in which the targets of newly synthesized compounds were largely unknown. Certain microorganisms having a similar genetic material sequence like human. These sequences thereby exclude potential mechanism-based toxicity of new antibacterial agents. Without the target identity and possible knowledge of genetic material overlap with a human target, it was difficult to design the structure-activity relationships of compounds that were being developed.

The genetic revolution in late 1990s led to identify the new targets that could yield new classes of antimicrobial compounds that are vulnerable to the present resistance mechanisms. The availability of complete genome sequences allows us to identify proteins that are conserved across the medically important pathogens.

The first sequence of an entire bacterial genome was determined in 1995. By,1997 complete genome sequences were publicly available for at least 11 organisms, including Esherichia coli, Bacillus subtilis and Saccharomyces Cerevisia. Today, more than 100 completed bacterial genomes are available in public databases.

The use of comparative genomics to identify protein targets that are candidates for antibacterial drug discovery. Validate essential proteins as antimicrobial targets. The whole-cell screening strategies are obtained by genetic assays.

Some medically important bacterial pathogens

Organism	Disease	Genome Reference size(Mb)
Gram-positive cocci Staphylococcus aureus	Skin and wound infections,septicemia, endocarditis and toxin-associated syndromes	2.8
Streptococcus pneumonia	Respiratory	2.2
Enterococcus saphaecalis	Bacteria, endocarditis and urinary-tract infections	3.2
Myoplasma pneumonia	Respiratory	0.8
Gram-negative cocci Pseudomonas aeruginosa	Opportunistic disease	6.3
Haemophilus influenza	Respiratory	1.8
Neisseria gonorrhoea	Sexually-transmitted disease	2.2
Helicobacter pylori	Gastrointestinal	1.7
Samlonella entiriditi	Gastrointestinal and typhoid	4.8
Eschericia coli	Gastrointestinal and urinary-tract infections	4.6
Mycobacterial disease Mycobacterium tuberculosis	Tuberculosis	4.4

TUBERCULOSIS

Tuberculosis, one of the most common infections, is caused by Mycobacterium tuberculosis. According to the World Health Organization (WHO), nearly one third of the world's population has been exposed to the tuberculosis pathogen. There are a number of known factors that make people

more susceptible to tuberculosis infection worldwide, the most important of which is human immunodeficiency virus (HIV). The association of tuberculosis with HIV infection is so dramatic that in some cases, nearly two third of the patients diagnosed with the tuberculosis are also HIV-1 seropositive[83] . Smoking more than 20 cigarettes a day also increases the risk of tuberculosis by two- to four times[84] .

Unfortunately, Tuberculosis treatment has not seen much progress as Mycobacterium tuberculosis (Mtb) is a stubborn pathogen. The available treatment options are few depending on a relatively small set of chemotherapeutic agents, which includes the widely used front-line drugs like Isoniazid, Ethambutol, Rifampicin, and Pyrazinamide[85].

A number of anti-TB drugs are ineffective against TB because of the development of resistant strains. The limited effectiveness of current chemotherapy stems largely from the lengthy and complicated nature of first-line anti-TB drugs. The most problematic issue with the current TB regimen is insufficient adherence to the treatment course, attributable to its length, complexity and adverse effects, led to difficult- and expensive to-treat multidrug-resistant tuberculosis (MDR-TB).

Treatment for MDR-TB typically requires 18–24 months of combination therapy with second-line drugs which are less efficacious, more toxic and expensive than the first-line drugs [34]. In few regions, almost 20% of MDR-TB cases were classified as extensively drug-resistant tuberculosis (XDR-TB). The treatment options for XDR-TB are very limited as XDR-TB bacilli are resistant not only to isoniazid and rifampicin, but also to fluoroquinolones and aminoglycosides [35]. More recently, another definition of XDR-TB as MDR-TB resistant to any fluoroquinolone and at least one of the second-line drugs (Capreomycin, Kanamycin and Amikacin) used in TB treatment [36]. There are

serious adverse effects with most MDR-TB and XDR-TB drugs, such as nephrotoxicity and ototoxicity with aminoglycosides, hepatotoxicity with ethionamide and dysglycaemia with gatifloxacin. In few cases, XDR-TB has been shown aggressive form of TB, causing very high mortality.

The improvement in TB chemotherapy can be achieved by four primary goals:

(i) Shorten and simplify TB treatment

(ii) Improve efficacy, safety and reduce long-lasting therapy

(iii) Develop drugs for HIV-TB co-infection, which can be readily co- administered with antiretrovirals

(iv) Shorten therapy of latent TB infection .

Moreover, to effectively treat and control MDR- and XDR-TB patients, physicians and national TB treatment programs require regimens based on safer, tolerable and efficacious drugs having new mechanisms of action [86].

The Global Alliance for Tuberculosis (GATB) drug development was established to address this need. Its top priority is the development of a new agent that will shorten the duration of chemotherapy from the current 6 – 8 months to two months or less. Also new drugs with activity against Mycobacterium drug-resistant tuberculosis and latent tuberculosis are needed.

WHO has recently launched its innovative "End TB Strategy"[39], supporting the TB elimination strategy and the vision of a TB-free world with zero death, disease and suffering due to TB. The new strategy clearly supports universal access to high-quality MDR-TB diagnosis and treatment. However, since the market launch of rifampicin in the early 1960s, no new anti-TB drug has been specifically developed until recently. The need for new drugs and regimens is obvious[40].

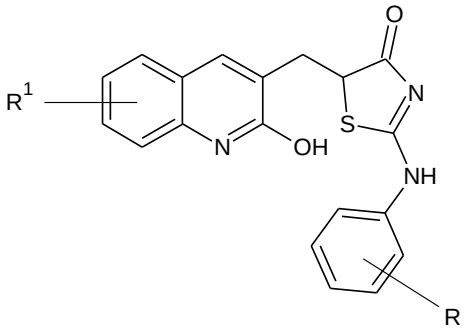
At present, the global TB development pipeline has nine candidates, but a key issue is how to develop them simultaneously in combination trials to identify the best candidate [41]. In this context, we try here to explore the ubiquitous heterocycle, coumarins based scaffold as promising antituberculars.

LITERATURE REVIEW

2-QUINOLONES

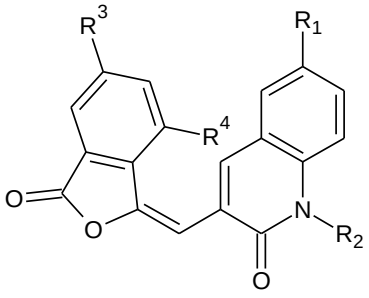
- Adithya.Adhikari et al.,synthesized a series of 5-(6-substituted -2-hydroxy quinolone-3-yl)methylidene[19].

Evaluated for antioxidant, antibacterial and antifungal activity. Compounds showed significant antioxidant properties.



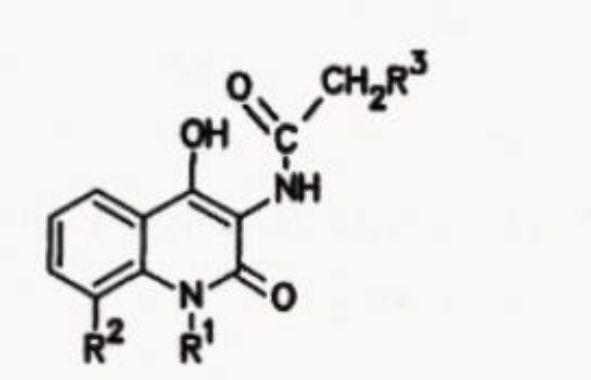
- Manish.P.Patel et al., 2014.,synthesized a series of aurones by aldol condensation of N(Un)substituted quinolone -3-carbalehyde.[22]

Compounds were screened *in vitro* for their antimicrobial activity against bacteria and fungal pathogens and also for their antioxidant properties, Majority were active against bacteria and fungi .3k ,3u showed antioxidant activity.



R_1 = H, CH_3, OCH_3, Cl; R_2 = H, allyl; R_3 = R_4 = H, OH

➢ Thomas kappe et al.,synthesized 3-acyl-4-hydroxy-2(1H)-quinolones With nitrogen bases via thermal beckmann rearrangement.(4)

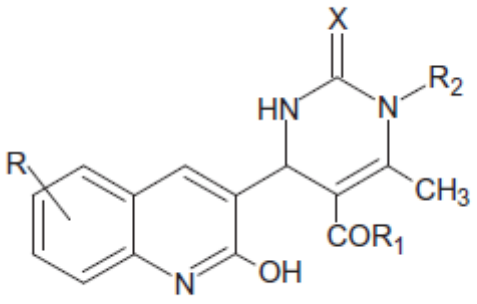


➢ Balakrishna Kalluraya et al., synthesized a series of dihydropyrimidine derivatives containing quinolones.[44]

The synthesized 4–(2-Hydroxyquinoline-3-yl)-5-carboxyethyl-6- methyl–pyrimidine-2-one were evaluated for their biological activity.all the synthesized compounds showed poor to good biological activity

R = H, CH3, OCH3 R1 = CH3, OC2H5 R2 = H, Ph

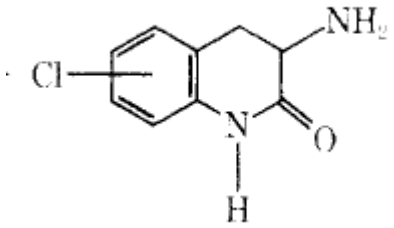
X = O, S



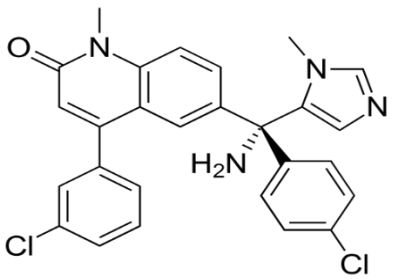
- Alvie L Davis et al.,synthesized a series of 3-amino-3,4-dihydro-l-hydroxycarbostyril by reductive cyclizations of the appropriately chloro-substituted o-nitrophenylalanines,[5]

The effects of a chloro substituent upon the microbiological activities of 3-amino-3,4-dihydro-l-hydroxycarbostyril were determined. 7-C1 analog was a more effective growth inhibitor than the parent unsubstituted compound.[5]

5-Cl,6- Cl,7- Cl,8- Cl



- Xue Wie Liu et al.,synthesized tipifarnib and proved Quinolinone derivatives were constructed via a Pd-catalyzed C−H bond activation/C−C bond formation/ cyclization cascade process with simple anilines as the substrates[47]

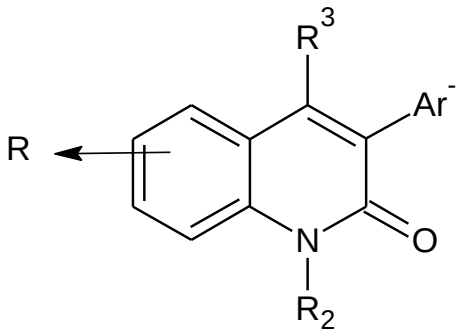


- Kang Zhao et al.,synthesized a series of 3‑Arylquinolin-2-ones. The reaction of the readily available N-methyl-N-phenylcinnamamides with phenyliodine bis(trifluoroacetate) (PIFA) in the presence of Lewis acids provides a general and efficient assembly of a variety of 3-arylquinolin-2-one compounds.[48]

R1=H,Me,OMe,F,Cl,Br,CF3,CO2Me

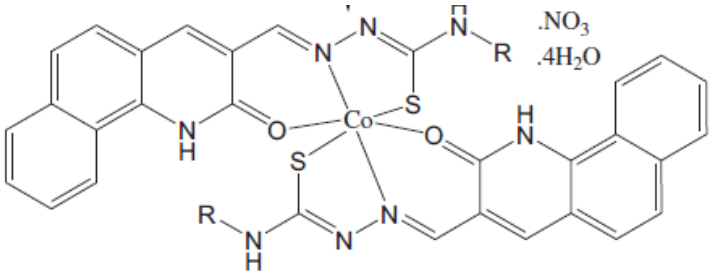
R2=Me,Bn,^{i}pr,cycloprpylmethyl

R3=H,R



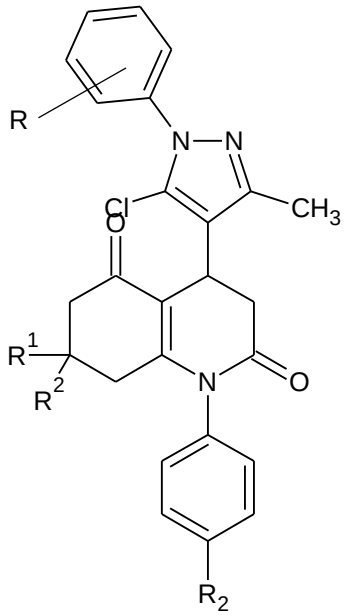
➢ Eswaran Ramachandran et al.,synthesized a series of new 2-oxo-1,2-dihydrobenzo[h]quinoline-3-carbaldehyde thiosemicarbazones[9]

Four new 2-oxo-1,2-dihydrobenzo[h]quinoline-3-carbaldehyde N-substituted thiosemicarbazone ligands and their corresponding new cobalt(III) complexes have been synthesized, characterized and evaluated for DNA binding, antioxidant and cytotoxic activity. The compounds showed significant antioxidant activity and higher cytotoxic activity with lower IC50 values indicating their efficiency in killing the cancer cells even at very low concentrations.



➢ Manish P Patel et al.,synthesized a new series of 12 derivatives of 4-pyrazolyl-N-arylquinoline-2,5-dione were synthesized by one pot base catalyzed cyclocondensation reaction[12].

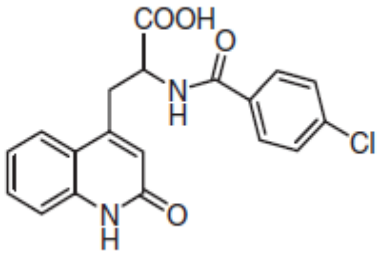
All the compounds were characterized by elemental analysis and screened, for their antimicrobial activity against six bacterial pathogens, Some of the compounds were found to be equipotent or more potent than commercial drugs, against most of the employed strains, as evident from the screening data.(10)



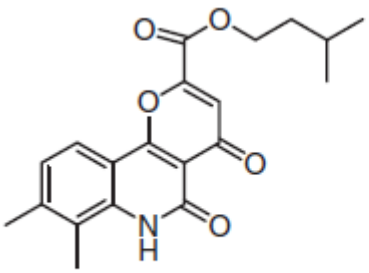
Compd	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l
R	H	3-Cl	4-Me	H	3-Cl	4-Me	H	3-Cl	4-Me	H	3-Cl	4-Me
R_1	H	H	H	Me	Me	Me	H	H	H	Me	Me	Me
R_2	F	F	F	F	F	F	OMe	OMe	OMe	OMe	OMe	OMe

- Stephen heeb reviewed an article quinolones to antibiotics and autoinducers[63]

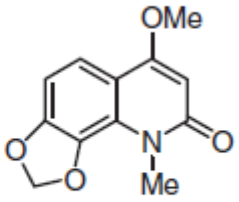
A wide variety of quinolone compounds have been discovered, several of which possess medicinally interesting properties ranging from antiallergenic and anticancer to antimicrobial activities.



Rebamipide



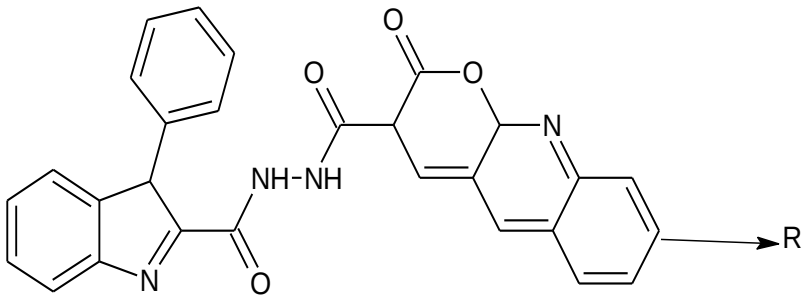
Repirinast



Casimiroine

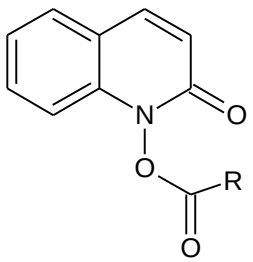
➢ BENNIKALLU HIRE MATHADA et al., synthesized some of 5-Substituted-3-phenyl-Nb- (Substituted-2-oxo- 2H-pyrano [2,3-b]quinoline-3-carbonyl)- 1H-indole-2-Carboxyhydrazide.

All the newly synthesized compounds were confirmed by spectral data and have been screened for their antibacterial activity, antifungal activity and antituberculosis activity and major compoungs showed promising antimicrobial,antifungal and antimycobacterial activity[53]

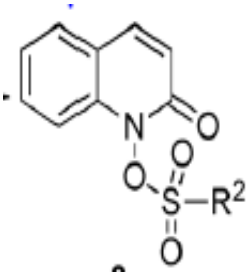


	a	b	c	d	e	f	g	h	i	j
R =	- Cl	-Cl	-Cl	-Cl	-Cl	$-OCH_3$	$-OCH_3$	$-OCH_3$	$-OCH_3$	$-OCH_3$
R'=	- H	-7-Br	$-7-CH_3$	$-9-CH_3$	$-9-OCH_3$	-H	-7-Br	$-7-CH_3$	$-9-CH_3$	$-9-OCH_3$

➢ N D Pradeep singh demonstrated a new class of carboxylate and sulfonate esters of 1-hydroxy- 2(1H)-quinolone as nonionic photoacid generators (PAGs).[64] Sulfonates of 1-hydroxy- 2(1H)-quinolone were found to be stable at room temperature Irradiation of carboxylates and sulfonates of 1-hydroxy-2(1H)-quinolone in aqueous methanol (l_310 nm) generated the corresponding carboxylic and sulfonic acids in good quantum yields.



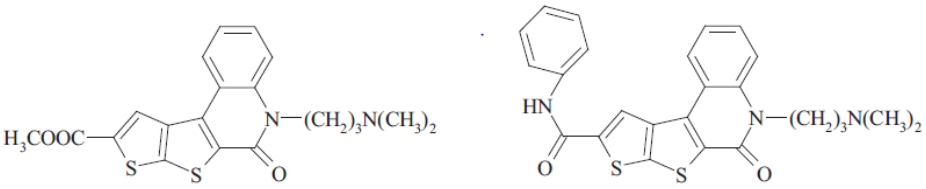
R1=5a=CH2CH2C10 ,5b=C6H5 5c=p-MeC6H4, 5d=p-MeOC6H4, 5e=p-NO2C6H4



$R^2 = CH_3$ (**8a**), C_4H_9 (**8b**), C_6H_5 (**8c**),
p-MeC_6H_4 (**8d**), *p*-$NO_2C_6H_4$ (**8e**)

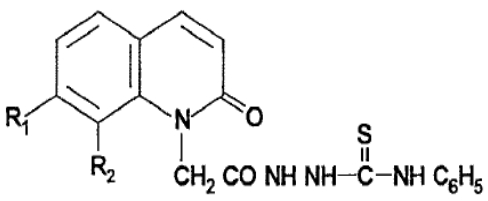
➢ Ankur Vaidya et al., reviewed on current developments of quinoline-based anticancer agents. [65]

Synthesized compounds 4,5)thieno(2,3)-quinolone derivatives Compound onleft showed best anticancer activity while compound on right shows least anticancer activity against.



➢ M B Deshmukh et al.,synthesized a series of N'-Acetylehydrazido qumoIin-2(lH) ones

The synthesized compounds were screened for their antitumor activity [54]



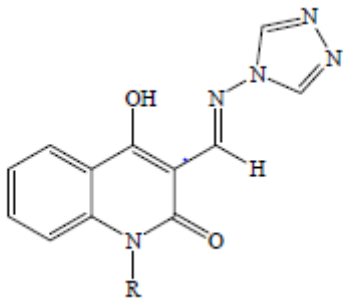
$R_1 = H, Cl$, $R_2 = CH_3$, H

LITERATURE REVIEW OF SCHIFF BASE

Antimicrobial activity

- Creaven B S et al., 2010 synthsized a series of quinolin-2(H)-one-triazole derived schiffs base.

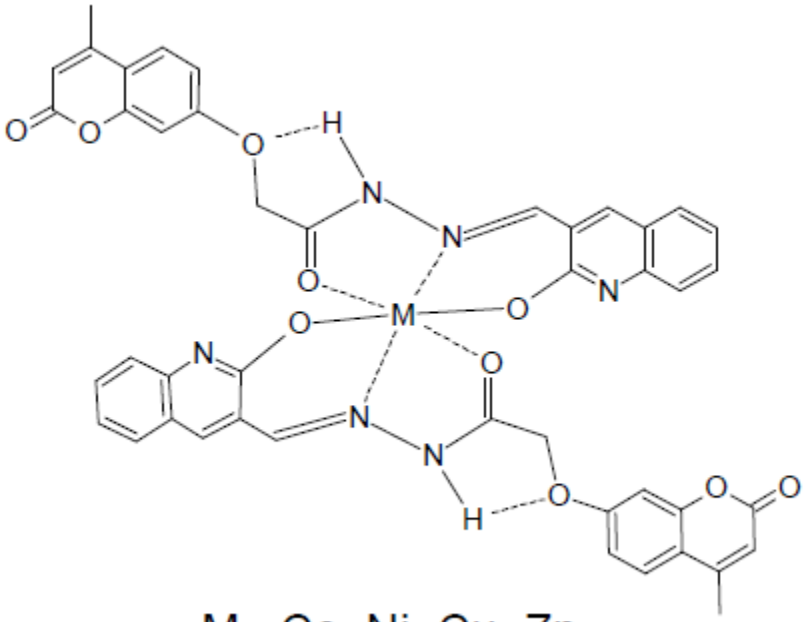
A series of quinolin-2(H)-one-triazole derived schiffs base ligand were synthesized by aldol condensation of 4-amino-1,2,4-triazole with N-substituted-3-formyl-4-hydroquinolin-2-(1H)-one. The synthesized compounds have been tested for their antimicrobial activity against gram positive, gram negative bacteria and fungal strains.



R = H, CH3, C2H5

- Pulin nath et al.,synthesized a series of Co(II), Ni(II), Cu(II) and Zn(II) complexes of Schiff bases of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy] acetohydrazide(OHQZ)[33]

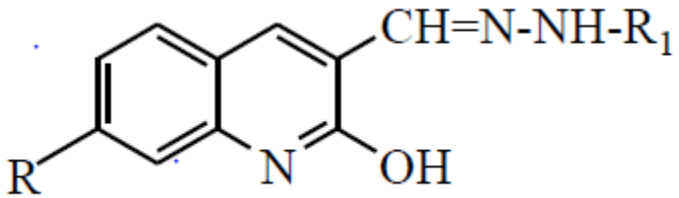
A series of Co(II), Ni(II), Cu(II) and Zn(II) complexes of Schiff bases of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy] acetohydrazide(OHQZ) have been screened for their antibacterial, antifungal and DNA cleavage studies



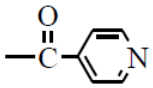
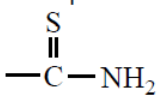
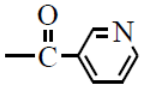
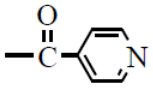
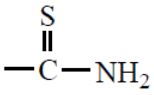
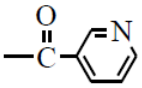
M= Co, Ni, Cu, Zn

➢ M.R.Pradeep kumar synthesized a series of substituted hydrazides yielded the novel schiffs bases of quinolones .[11]

All the synthesized compounds were screened for invitro antifungal activity by serial dilution method. The preliminary antifungal activity screening result of these compounds depicted them as potential antifungal leads endowed with moderate to excellent activity.

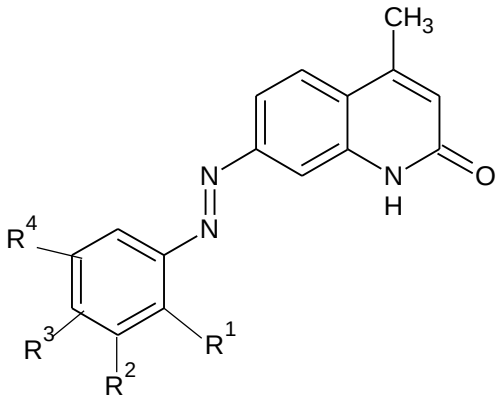


Where,

	R	R_1		R	R_1
II a =	F		II d =	F	
II b =	F		II e =	NO_2	
II c =	NO_2		II f =	NO_2	

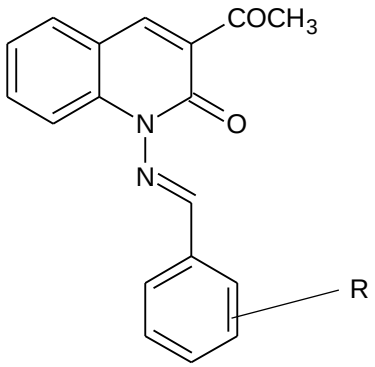
➢ Jayashree B.S et al.,synthesized a series a 10compouds of schiffs bases of 7-amino-4-methyl carbostyrils b Conrad- limpach synthesis .[41]

They all were evaluated for their antibacterial activity by agar diffusion method.out of ten, four compounds showed good antibacterial activity against both gram positive and gram negative organisms.



➢ Abishek Kumar et al., A series of novel substituted 3-acetyl-1 (benzylideneamino) quinolin-2(1H)-one (1-12) have been synthesized by condensing different substituted3-acetyl-1-amino-quinolin-2-one and aromatic aldehydes in alcohol medium[68].

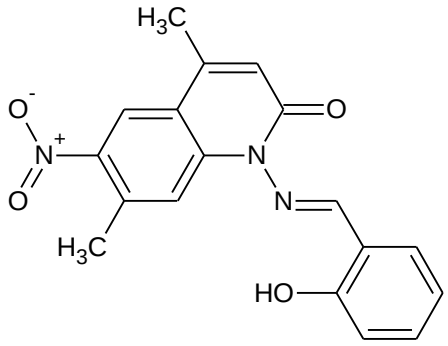
The synthesized compounds were screened for their antimicrobial, antioxidant and cytotoxicity activities. And concluded that most of the synthesized compounds showed good antimicrobial activity and few compounds showed good antioxidant and cytotoxicity activity.



R: H, 6-NO2, 6-Cl, R1: 3-NO2, 3,4,5-OCH3, 4-CH3, 4-OH, 2-Cl, 2-NO2

- Redha I. Al-Bayati et al.,synthesized a new schiffs base 1-[(2-hydroxy-benzylidene)-amino]- 4,7-dimethyl-6-nitro-1H-quinolin-2-one and screened for its antimicrobial activity.[62]

1-amino-4-7-dimethyl-6-nitro-1H-quinoline-2-one was reacted with salicyaldehyde to synthesize the corresponding Schiff base. and resulted that synthesized compounds showed no activity.



➢ K Siddapa et al ., synthesized a new complex of 3-[(2-hydroxyquinoline-3ylmethylene)-amino]-2-methyl-3-H-quinazolin-4-one[67]

The synthesized compounds were characterized by spectroscopic methods and tested for their antimicrobial activity against selected bacteria and fungi and found that metal complexes are much more potent against antimicrobial pathogens in comparision to free Schiff base ligand.

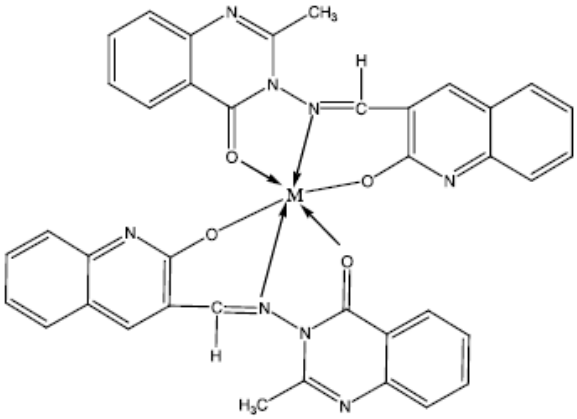
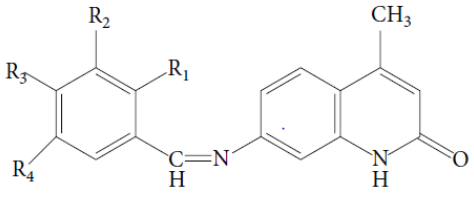
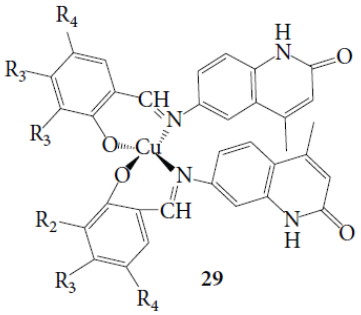


Fig. 3. M=Cu(II), Co(II), Ni(II) and Mn(II)

➢ Anu Kajal et al.,reviewed various Schiff bases and those compounds were evaluated for their various biological activities such as anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, antiglycation, and antidepressant activities[31]



28



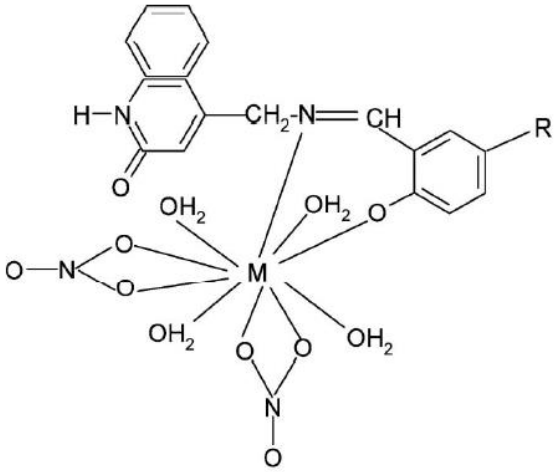
29

28, 29	R_1	R_2	R_3	R_4
d	OH	OC_2H_5	H	H

Antitumor activity

➢ Shreedhar D. Dhumwad et al., synthesized a series of La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III) and Dy(III)complexes have been synthesized with Schiff bases derived from 4-aminomethylcarbostyril and substituted salicylaldehyde.and screened for their antitumour activity.[8]

In that biological studies, some of the compounds have shown promising results. The in vitro antitumor study of the complexes reveals that the activity of Lanthanide(III) complexes increases at lower concentrations.

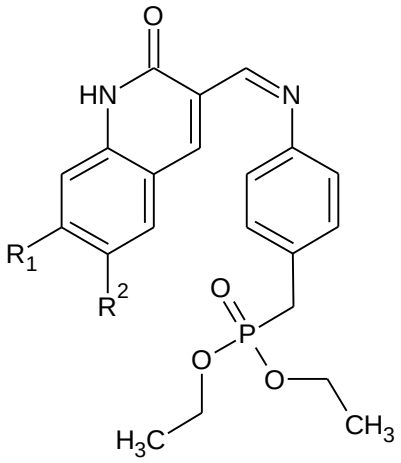


R=H, OCH_3, Cl

M=La, Ce, Pr, Nd, Sm, Eu, Gd & Dy

➢ Xian-li Ma et al., designed and synthesized a set of 2-oxo quinoline aminophosphonate by kabachnik-fields reaction.[81]

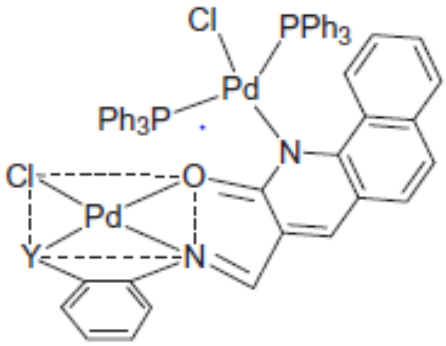
The synthesized a set of 2-oxo quinoline aminophosphonate compounds were evaluated for their antitumor agents.the compounds were found to exhibit a novel antitumor activity.



5a=R1=R2=H,5b=R1=CH3,R2=H,5c=R1=OCH3,R2=H,5d =R1=R2=CH2OCH2

➢ Karupannan natarajan et al.,synthesized a series of novel binuclear Pd(ll) complexes of 2-oxoquinoline-3- carbaldehyde Schiff bases.[36]

The newly synthesized novel binuclear Pd(ll) complexes of 2-oxoquinoline-3- carbaldehyde Schiff bases were characterized by elemental analysis ,spectroscopic technique and and its catalytic efficiency was tested for N-arylation of imidazole.

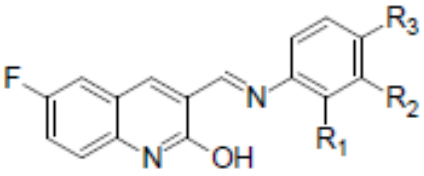


(Y = O or S; R = H or CH.

Antimycobacterial activity

➢ Mustapha C. Mandewale et al.,synthesized a new series of 6-fluoro-2-hydroxyquinoline-3-carbaldehyde.[35]

The newly synthesized schiffs bases and their Zn(ll) and Cu(ll) complexes were evaluated for their anti-tubercular activity.Zn(ll)metal complex showsbetter fluorescence as well as anti-tubercular activity than Cu(ll).

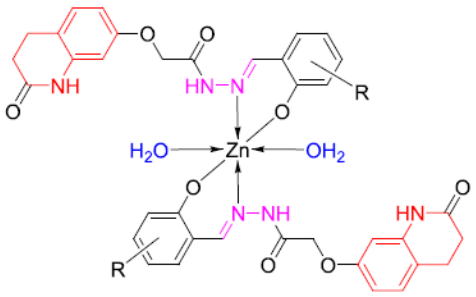


[SB 01-SB 10]

A/SB	R_1	R_2	R_3
01	H	H	F
02	F	Cl	H
03	CF_3	H	H
04	H	CF_3	H
05	H	CF_3	CN

➢ Santhosh kokate et al., 2016 synthesized a series of hydrazone derivatives 2-(2-oxo-1,2,3,4-tetrahydroquinoline-7-yloxy)acetohydrazide.[10]

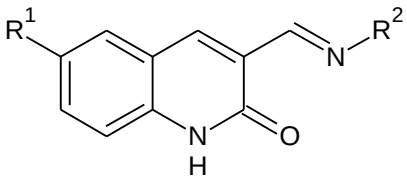
They were prepared from 7-hydroxy-3,4-dihydroquinolin-2(1H)-one as starting material. Then the condensation of 2-(2-oxo-1,2,3,4-tetrahydroquinoline-7-yloxy)acetohydrazide with different o-hydroxyaldehyde derivatives yielded into hydrazone derivatives . These hydrazone ligands were complexed with Zn (II) yielded complexes and screened for their antitubercular activity.synthesized compounds 6c, 6e, 6h proven as efficient antitubercular agent.



Antioxidant Activity

➢ Xianghui Yi et al aynthesized a series of 2-oxo-quinoline-3-carbaldehyde derived Schiff bases[48] .

The compounds were synthesized based on the 2-oxo-quinoline structure core as novel antioxidants. The synthesized compounds were evaluated for their antioxidant activity. The results showed that IC50 of most compounds were lower than standard value 10 mg/mL, indicating good antioxidant activities of these compounds.



R^1	R^2
H	OH
CH_3	OH
H	C_4H_9
CH_3	C_4H_9
H	CH_2Ph
CH_3	CH_2Ph
H	CH_2CH_2OH
CH_3	CH_2CH_2OH
H	*o*-OH-C_6H_4
CH_3	*o*-OH-C_6H_4

PURPOSE AND PLAN OF WORK

Infectious diseases are most devastating diseases all over the world. They are mainly caused by various infectious micro-organisms. All these infections may cause illness and in some cases lead to death of patients. There are many ways to get the infectious diseases, but in all the cases we are not able to prevent the infections that spread. Every year millions of people are prone to infectious diseases and death rate is also getting fluctuation due to the intensity of easily spreading character of the microorganism.

To overcome this all the major pharmaceutical companies are involved in extensive research work to generate powerful antibodies against the drastic disease causing agents. Although there are potent antibiotics are present in market. But day to day there is a need for new potent antibiotics, because the microorganism are getting resistant to the drugs by adopting themselves to withstand the potency of the drug ,by mutation, membrane permeability and spore formation.

The spread of drug-resistant TB is a man-made tragedy, caused by inadequate or incomplete treatment for decades, old drug regimen that takes atleast six months to cure TB. Drug resistant strains emerge when bacteria are sporadically exposed to existing drugs, or when patients are unable to complete the lengthy and burdensome treatment.

Multidrug-resistant TB(MDR-TB)is defined by resistant to atleast two of today's four standard first-line drugs. The World Health Organization (WHO) estimates that there are nearly a half-million new cases of MDR-TB each year. These cases are difficult to manage and have much lower cure rates. For MDR-TB patients, treatment can take upto 2 years, with second line drugs that are more expensive, do not always work, and have significant side effects.

However, only a limited effort has been made to develop new active chemical entities or rapid diagnostic tests, and their relevance to the global TB control has been questioned.

Combinations of two or more active moieties into one is a common procedure for getting the synergistic effect to enhance the drug activity with less dose of drug.

Quinolones is a most important heterocyclic moiety which exhibits remarkable pharmacological activities. Literatures also indicates that the compounds having quinolone nucleus have a wide range of therapeutic uses that include anti-bacterial , anti-inflammatory ,antiviral, anti-tubercular , anticancer activities.

3-formyl-2-quinolone and substituted 3-formyl-2-quinolones ,isoniazid based Schiff bases have been reported to posses antimicrobial properties, hence the synthesized compounds were screened for their in-vitro antimicrobial activity against selected strains of gram positive , gram negative bacteria and fungi and for their antimycobacterial activity against strain mycobacterium tuberculosis H37RV.

The present work consists of the following different stages:-

Phase I : Literature review

Phase II : Synthesis of various Schiffs bases

Phase III : Spectral studies of their synthesized compounds

Phase IV : Antimicrobial screening of synthesized compounds

Antimycobacterial studies

Antibacterial studies

Antifungal studies

CHEMISTRY

VILSMEIR HAACK REACTION [1]

In 1927 Vilsmeier and Haack observed that N-methylformanilide can formylate aniline derivatives in the presence of POCl3.1 Later the reaction was extended using simple formamide derivatives like N,N-dimethylformamide, N-formylpiperidine, N-formylmorpholine *etc.* to formylate electron rich aromatic and aliphatic substrates, and these types of reactions are known as Vilsmeier-Haack reactions.2 A Vilsmeier- Haack reagent **3** is produced when a disubstituted formamide or amide, typically N,N-dimethylformamide (DMF) **1** is treated with an acid halide, frequently phosphorous oxychloride, though to a lesser extent, oxalyl chloride .

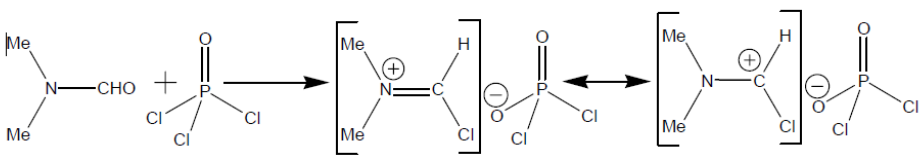
Synthetic Method

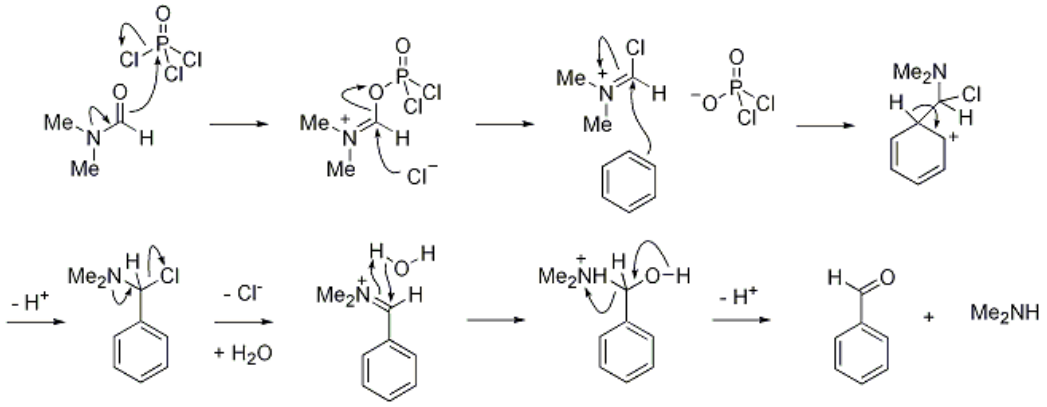
There have been a number of practically important routes to synthesise of 2-chloroquinoline-3-carbaldehydes and one among them is Vilsmeier-Haack reaction of acetanilides

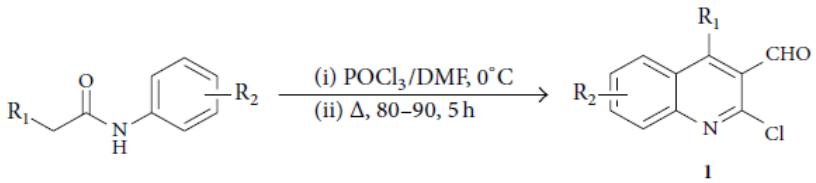
1. Vilsmeier-Haack reaction

2-Chloroquinoline-3-carbaldehydes **2** were synthesized from acetanilides **1** *via* a Vilsmeier-Haack reaction either by traditional methods or by microwave or ultrasonic irradiation.

Mechanism:





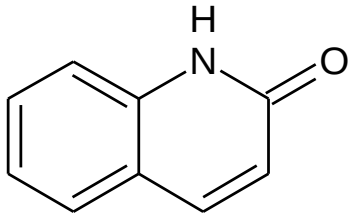


R_1 = H, COMe; R_2 = H, alkoxy, halogen

QUINOLONES

Quinolones are molecules structurally derived from the hetero bicyclic aromatic compound quinoline, the name of which originated from the oily substance obtained after the alkaline distillation of quinine (Gerhardt, 1842). Since the isolation of quinine from Cinchona bark in 1811, many other quinoline derivatives have been isolated from natural sources. In particular, 2-hydroxy quinoline and 4-hydroxyquinoline, which predominantly exist as 2(1H)-quinolone and 4(1H)-quinolone, respectively, and form the core structure of many alkaloids, were isolated from plant sources. Several different animal and bacterial species also produce compounds of the quinolone class.

It is a 2-ring condensed heterocyclic compound containing N as hetero atom,and contains several positions that can be replaced by arbitrary substituent groups and is used as a chemical building block, scaffold, fragment, and pharmacophore in drug design or discovery.2 quinoline is an organic compound related structurally related to quinolone.It is the majority tautomer in equilibrium with 2-quinolinol.The compound can be classified as a cyclic amide,and as such is used as a isostere for peptides and other pharmaceutically-inspired targets.The isomer 4 quinoline is the parent of a large class of quinolone antibiotics.

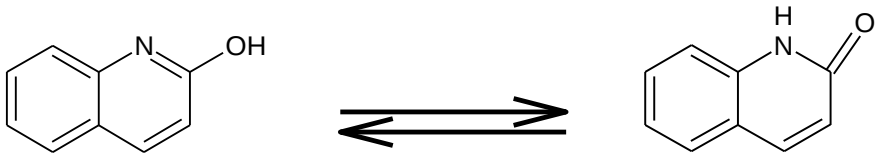


Other names:

Carbostyril

1,2-dihydroxy-2-oxoquinoline

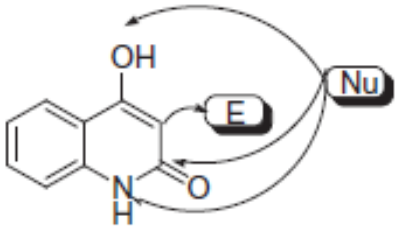
1H-quinolin-2-one



2 quinolone(right)and its tautomer 2-hydroxyquinoline (left)

Chemical reactivity[6]

It is evident from the topography of 4-hydroxy-2(1H)- Quinolone.That it possesses both electrophilic and nucleophilic properties. The third position in the 4-hydroxy- 2(1H)-quinolone ring is highly activated, because of the influence of the hydroxyl group with electron-donating properties and electron-withdrawing effects of carbonyl oxygen atom at the second place. There is a conjugation of p-electrons from the double bond and lone p-electron pairs from oxygen atom. These factors make the third position in the quinolone ring very convenient for many reactions. Thus reactions like coupling and halogenation reactions have taken place readily at such carbon. Recently Michael type addition was also described. The oxygen atom of the hydroxyl group however remains the main site for attack by acylating and alkylating agents. It seemed that hard nucleophiles attack preferentially oxygen atom and somewhat nitrogen atom, while the soft ones attack preferentially the carbon atom

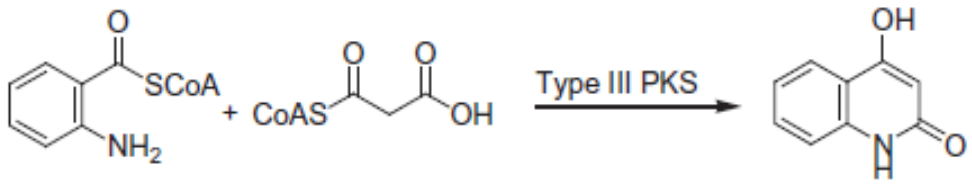


Chemical reactivity of 4-hydroxy-2(1*H*)-quinolone.

SYNTHESIS [6]

BIOSYNTHETIC PATHWAY

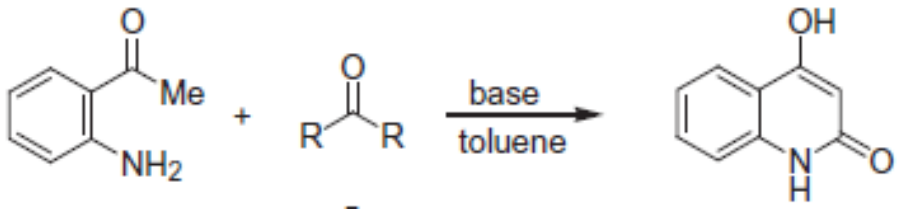
Biosynthesis of 4-hydroxy-2(1H)-quinolone 1 involves benzalacetone synthase from Rheum palmatum efficiently catalyzed the condensation of anthraniloyl-CoA 2 with malonyl- CoA 3 to produce 4-hydroxy-2(1H)-quinolone, a novel alkaloidal scaffold produced by a type III polyketide synthase (PKS).



SYNTHETIC PATHWAY

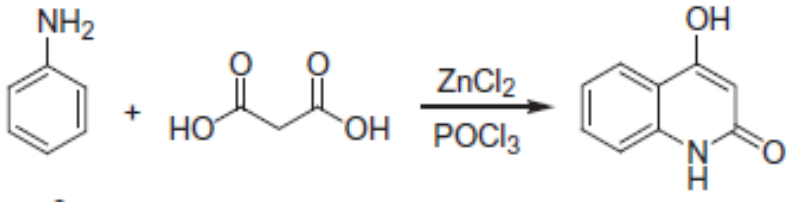
There are several methods for the synthesis of 4-hydroxy- 2(1H)-quinolone . The following are some of the methods which have been used to prepare 4-hydroxy- 2(1H)-quinolone.

1) The reaction of 2-aminoacetophenone with acylating agents such as phosgene, dimethylcarbonate, or diethylcarbonate in the presence of stoichiometric amount of base in anhydrous toluene afforded 4-hydroxy-2(1H)-quinolone 1 in variable yields. It was found that sodium hydride was a more effective base than sodium ethoxide.

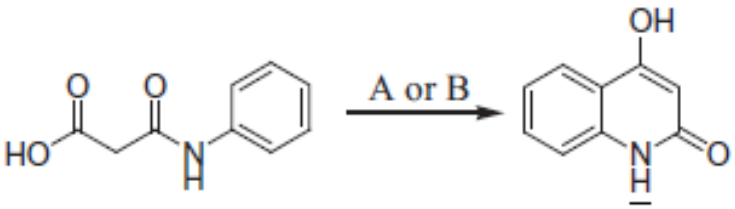


2) Condensation of aniline 6 with malonic acid 7 in the presence of a mixture

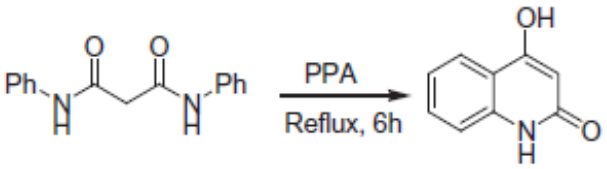
of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent furnished. This environmentally unacceptable procedure suffers from many disadvantages like long reaction period, use of dehydrating agents ($ZnCl_3$) and hazardous reagent ($POCl_3$). Recently, it was found that, the yield was improved to be carried out under microwave condensation in the presence of N,N-dimethylformamide, which acts as an energy transfer agent and homogenizer to increase the reaction



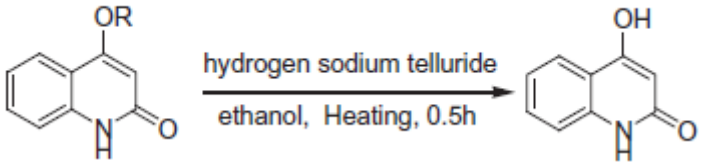
3) Intramolecular cyclization of malonic acid monophenyl amide to form 4-hydroxy-2(1H)-quinolone is a convenient procedure; the crucial problem to be solved is to reduce or eliminate the decarboxylation of the intermediates. Thus, Eaton's reagent (phosphoric anhydride and methyl sulfonic acid) or polyphosphoric acid (PPA) was chosen as cyclization reagents in mild reaction condition The synthesis of 4-hydroxy-2(1H)-quinolone 1 is also observed via cyclization of N,N-diphenyl malonamide in the presence of polyphosphoric acid (PPA) at 140–150° C.)



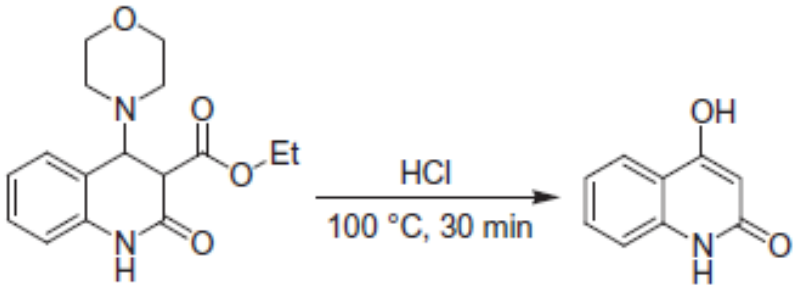
A=Eatons reagent,70°c ,B=PPA,140^0 C



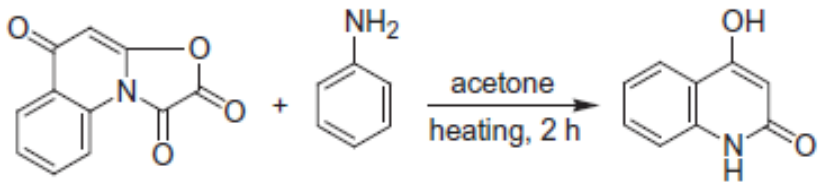
5) Shobana et al. have described an efficient procedure for the synthesis of 4 hydroxy quinolone via the cleavage of 4-allyl quinoloneyl ether or quinoloneyl ethyl carbonate using a catalytic amount of hydrogen sodium telluride in acetic acid and ethanol.



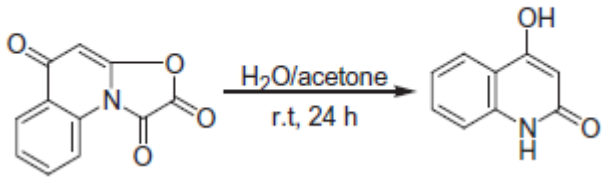
6) Short term (30 min) boiling of the ethyl ester of 4-morpholino- 2-oxo-1,2-dihydroquinoline-3-carboxylic acid 11 in concentrated hydrochloric acid afforded 4-hydroxy-2(1H)-quinolone.



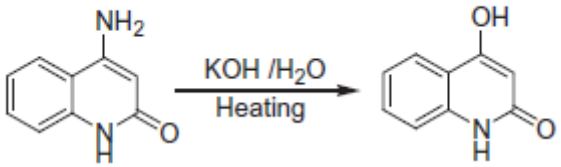
7) Aminolysis of oxazoloquinolone with aniline under heating in acetone for two hours gave 4-hydroxyquinolone 1 in 83% yield



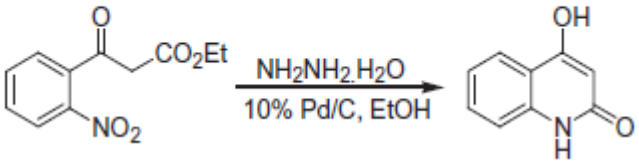
8) Similarly, oxazoloquinolone was easily hydrolyzed by a mixture of acetone/water at room temperature to give 4- hydroxyquinolone 1 in 90% yield



9) 4-Amino-2-hydroxyquinoline on heating with aqueous potassium hydroxide was smoothly hydrolyzed and converted into 4-hydroxyquinolone



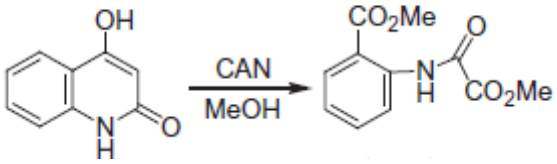
10) The reduction of ethyl 3-(2-nitrophenyl)-3-oxopropanoate 13 with hydrazine hydrate and 10% Pd/C in ethanol at 23^0c and subsequent cyclization lead to the formation of quinolone in 86% yield . Also, this reduction can be successfully carried out by means of hydrogen in the presence of platinum black catalyst



REACTIONS OF 2-QUINOLONES

Reactions involving cleavage of lactam ring

Reaction of with two equivalents of cerium(IV) ammonium nitrate (CAN) in methanol at room temperature afforded methyl-N-(2-methoxycarbonylphenyl) oxalamate as the sole product in 94% yield

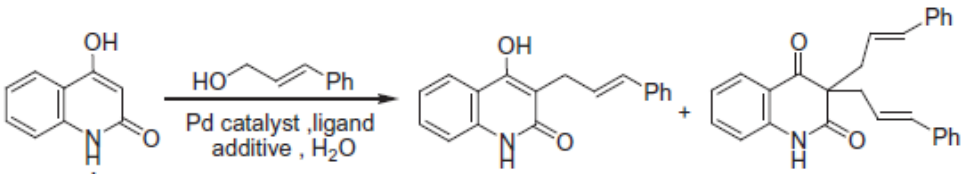


Reactions involving carbon–carbon bond formation

C-C Bond formation

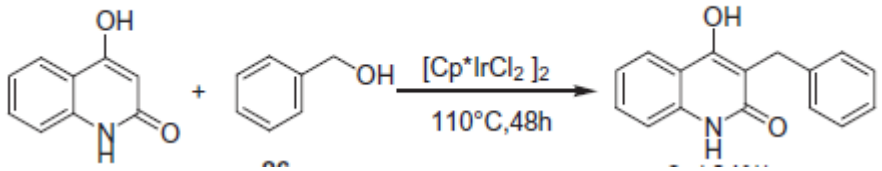
C3-Allyation reaction.

The allyation of 4-hydroxy- 2(1H)-quinolone 1 is an important strategy for the formation of C–C bonds in organic synthesis. Synthesis of allyl and benzyl-substituted 4-hydroxy-2(1H)- quinolone compounds. Activator-free and one-pot C-allylation of 4-hydroxy- 2(1H)-quinolone by simple palladium catalyst in water is now a well-documented process . Palladium-catalyzed allyation of using cinnamyl alcohol directly gave the corresponding mono- and diallylated products



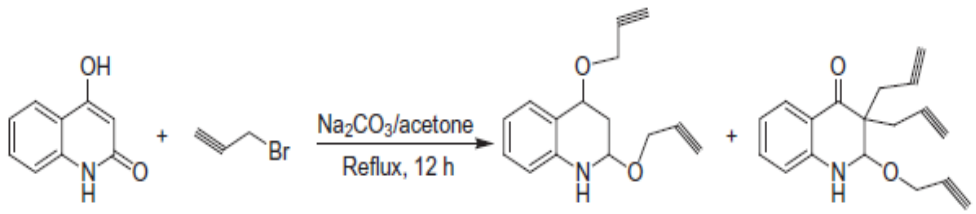
C3-Benzylation.

Iridium catalyzed alkylation of 4-hydroxy- 2(1H)-quinolone with benzyl alcohol under solvent free thermal condition afforded the corresponding 3-benzyl-4- hydroxyquinolin-2(1H)-one



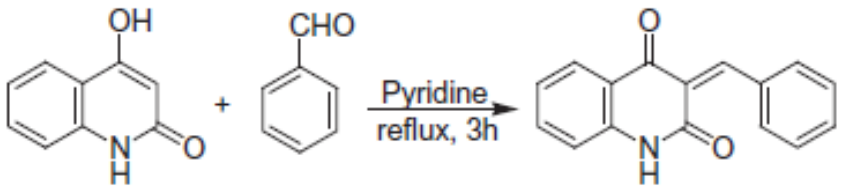
Propargylation and allenylation

Propargylation of 4- hydroxy-2(1H)-quinolone with propargyl bromide in the presence of anhydrous potassium carbonate, under reflux conditions for 12 h in acetone, afforded a mixture of O,O-dialkylated quinolone and C,C,O-trialkylated quinolone.

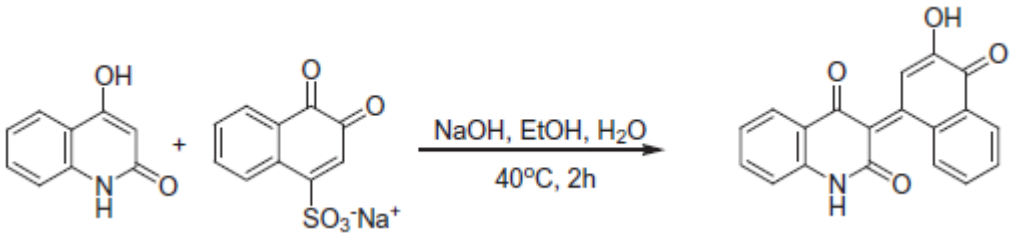


Olefination

One of the most successful strategies for constructing 3-benzylidene quinolone in only one diastereoisomeric form (Z) is the Knovenagel condensation. Heterocondensation reaction between 4-hydroxy-2(1H)-quinolone 1 and benzaldehyde in pyridine under gave (Z)-2,4-dihydro-3-benzylidenquinolin-2,4-dione.



Michael addition of with the sodium salt of 1,2-naphthoquinone-4-sulfonate in alcoholic sodium hydroxide at 40°C by crushing in a mortar or traditional heating gave 3-(3-hydroxy- 4-oxonaphthalen-1-ylidene)quinoline-2,4-dione

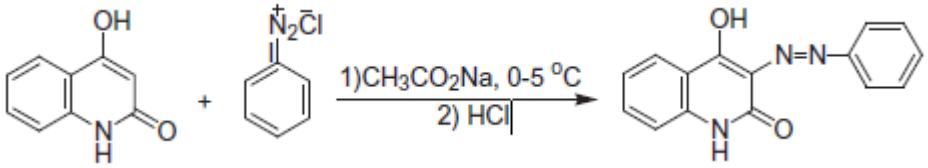


Reactions involving carbon-heteroatom bond formation

C–N Bond formation

Coupling reactions.

3-(2-Phenylhydrazono)quinoline- 2,4(1H,3H)-dione was prepared by coupling of basic solution (sodium acetate) of 4-hydroxy-2(1H)-quinolone with diazotized aniline .

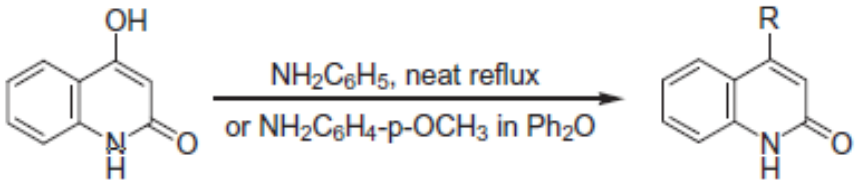


Nitration reaction.

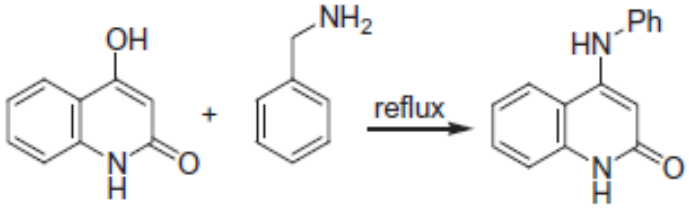
Nitration of with neat nitric acid or a mixture of glacial acetic acid and concentrated nitric acid afforded 4-hydroxy-3-nitroquinolin-2(1H)-one 3

Formation of substituted amine (Amination).

A simple and facile amination of with equimolar amounts of aniline (neat) or p-anisidine (in Ph2O) afforded 4-anilino-2-quinolinone a or 4-methoxy derivative , respectively

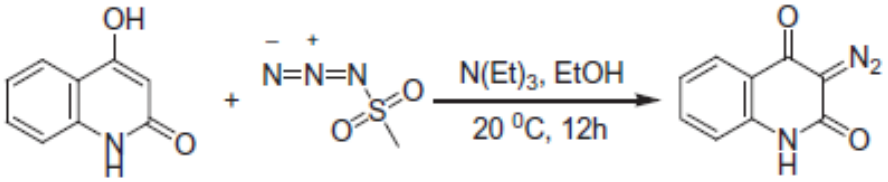


Stadlbauer and Kappe described the condensation of 1 with phenylmethanamine in various solvents under reflux condition which gave the 4-(phenylamino)quinolin-2(1H)-one



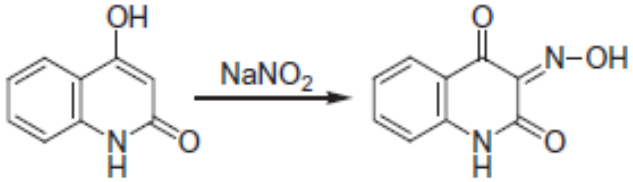
Formation of azide

The formation of 3-diazo-1H-quinolin- 2,4-dione is observed when 4-hydroxy-2(1H)-quinolone is reacted with mesyl azide in ethanol in the presence of triethyl amine.



Formation of oxime.

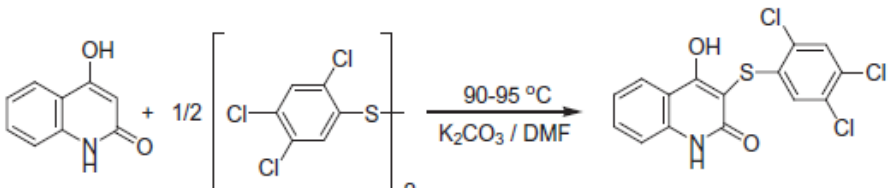
The main method for the synthesis of the quinolone oxime is based on the reaction of sodium nitrite with in the presence of acetic acid or hydrogen chloride.



C–S Bond formation

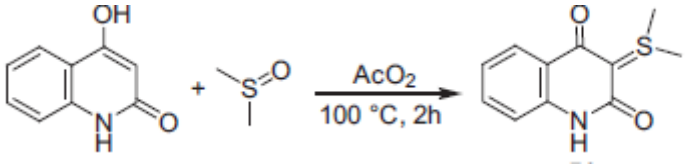
Sulfides (Thioethers) formation.

Treatment of 4-hydroxy-2(1H)-quinolone 1 with diaryl disulfides in dimethylformide in the presence of potassium carbonate yielded 4-hydroxy-1-methyl-3-(2,4,5-trichlorophenylthio)- 2(1H)-quinolone



Thionation reaction.

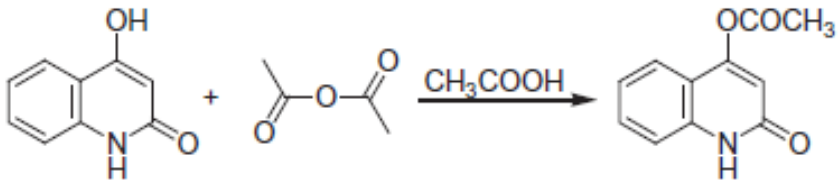
4-Hydroxy-2(1H)-quinolinone reacts with dimethylsulfoxide in acetic anhydride at 100 _C to afford 3-dimethylsulfonioquinoline-2,4-dionate as the main product .



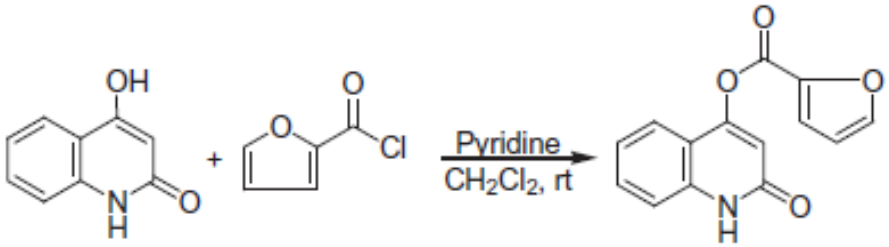
C–O Bond formation

Esterification.

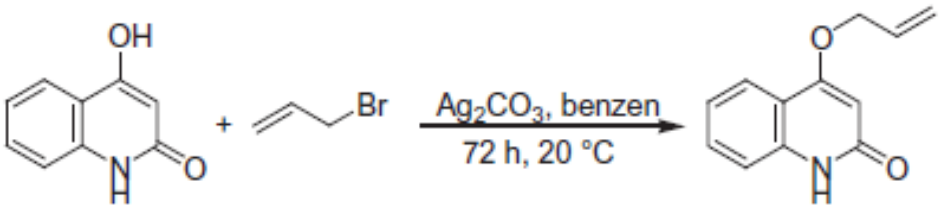
The direct esterfication of 4-hydroxy- 2(1H)-quinolone with acetic anhydride using triethylamine , pyridine or acetic acid afforded 4-acetoxyquinolin-2-one in good yield .



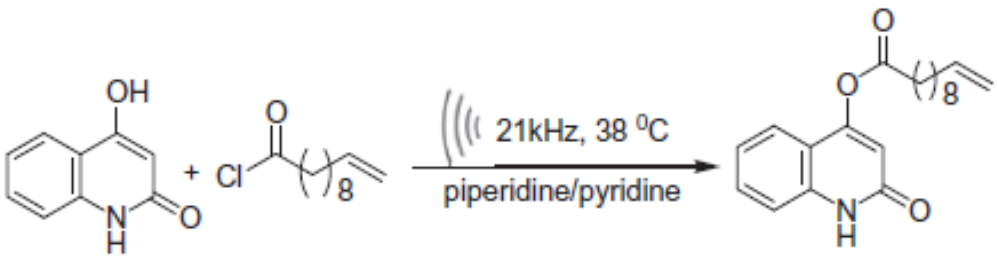
The esterification of 4-hydroxy-2(1H)- quinolone 1 with 2-furoyl chloride in pyridine and dichloromethane afforded 2-oxo-1,2-dihydroquinolin-4-yl-furan-2-carboxylate as human rhinovirus 3C protease inhibitors



4-Allyloxyquinolone was obtained by the reaction of 4- hydroxy-2(1H)-quinolone with allylic bromide and silver carbonate in benzene for 72 h at room temperature.

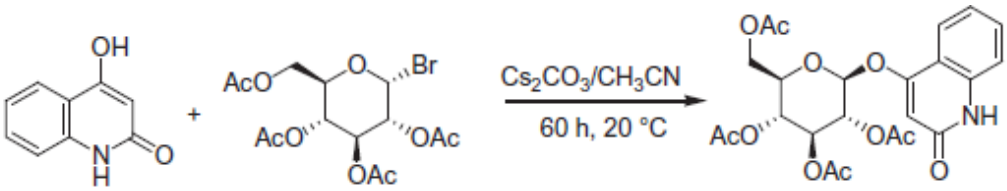


Acylation of 4-hydroxyquinolin-2-(1H)-one with undec- 10-enoyl chloride afforded 2-oxo-1,2-dihydroquinolin-4- ylundec-10-enoate .



Glucosylation reaction.

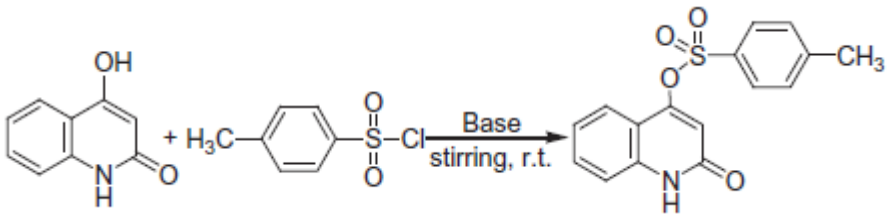
Selective glucosylation of 1 into 4-(b-D-glucopyranosyloxy)quinoline-2(1H)-one was proceeded via treatment of 1 with tetra-acetobromo-a-D-glucose in combination with cesium carbonate in acetonitrile at room temperature to give 4-(2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyloxy)- quinolin-2(1H)-one in 74% yield



Hetero ether formation

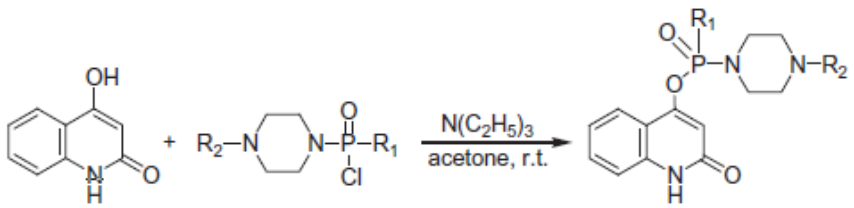
Sulfonate ether formation.

Two groups have reported the one step formation of 4-(p-toluenesulfonyloxy)-2(1H)-quinolone via tosylation reaction of 4-hydroxy-2(1H)-quinolone 1 with tosyl chloride in pyridine and 4-(N,N-dimethlyamino)pyridine or triethylamine in dichloromethane at room temperature



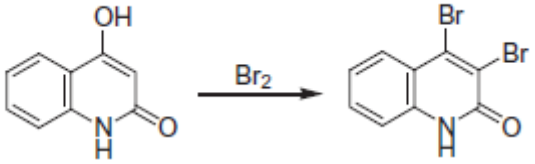
Phosphorylation reaction

A series of new piperazine phosphoramide derivatives of 4-hydroxyquinoline were synthesized through a facile phosphorylating reaction starting from 4-hydroxy-2(1H)-quinolone and various phosphorylating agents in the presence of triethylamine at room temperature

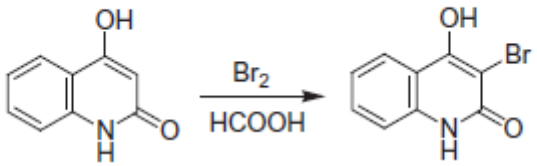


Bromination.

Bromination of 4-hydroxy-2(1H)-quinolone 1 with bromine in formic acid, acetic acid or phosphorus oxytribromide yields 3,4-dibromo quinoline 86 .

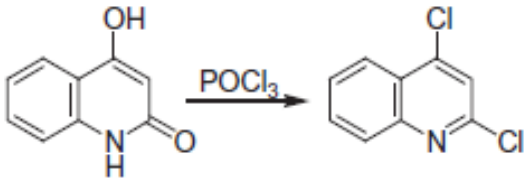


Gaston have repeated this reaction in formic acid, but isolated only 3-bromo-4-hydroxy-2(1H)-quinolone , the structure of which was firmly established by conversion into the known 3-bromo-2,4-dimethoxyquinoline



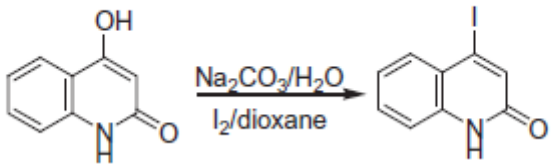
Chlorination

Chlorination of 4-hydroxy-2(1H)-quinolone with phosphorous oxychloride under reflux condition afforded 2,4-dichloroquinoline 88 in good yield . Also, microwave-assisted reaction using chlorophosphonium salt was examined for this reaction, and it shortened the reaction time (5 min) as compared with a thermal reaction



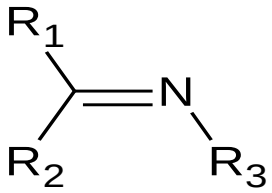
Iodination

Iodination of 4-hydroxy-quinolin-2(1H)- one with iodine in aqueous dioxane afforded 4-hydroxy-3- iodoquinolin-2(1H)-one in 83% yield



SCHIFFS BASE

INTRODUCTION[69,70,80]



R_1, R_2= alkyl,aryl or H

R_3= alkyl ,aryl

General structure of a Schiff base

Schiff bases are biologically as well as synthetically important nitrogen containing compounds having azomethine group (-CH=N-) and are formed by condensation between primary amines and carbonyl compounds.Schiff bases exhibits a broad range of biological activities including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral,anti-tubercular and antipyretic properties

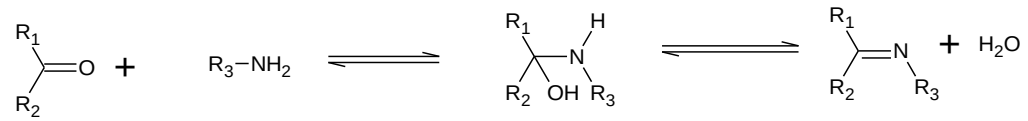
Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.

GENERAL METHODS FOR THE FORMATION OF C=N BONDS

a) Amine carbonyl condensations:

The classic method for the introduction of the carbon nitrogen double bond into the molecule involves the condensation of aldehydes and ketones with a variety of amino compounds (amines, hydroxylamines, hydrazines) followed by elimination of elements of water to give corresponding azomethines.

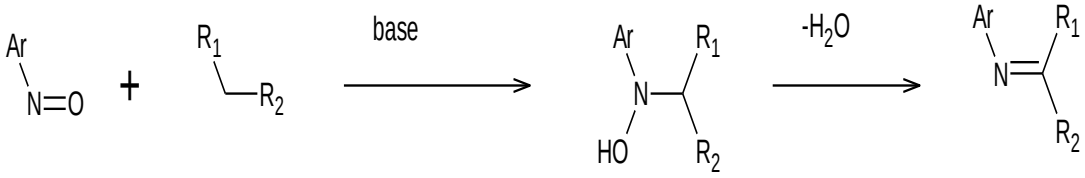


R_1,R_2= H, alkyl,aryl

R_3= alkyl, aryl, OH,OR,NHR

b) Condensation reaction involving active methylene compounds:

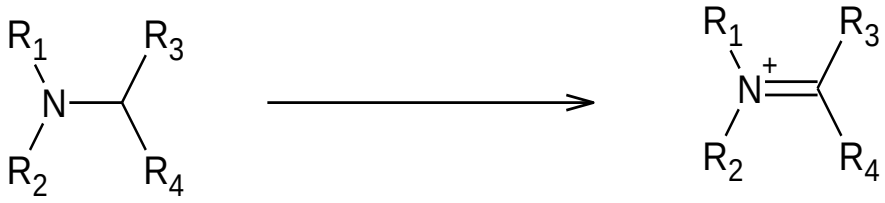
Aromatic nitroso compounds undergo base catalysed condensation with active methylene compounds to give intermediate adducts (hydroxylamine derivatives) which can be dehydrated to azomethines.



c) Dehydrogenation (oxidation) of amino compounds to azomethines:

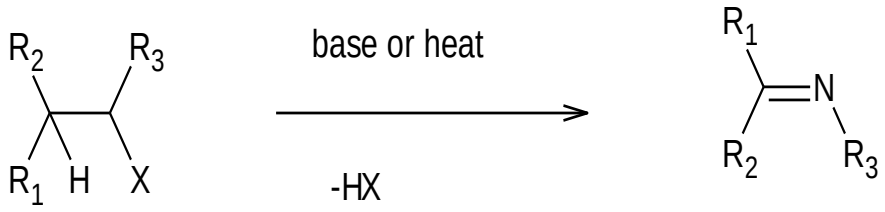
The dehydrogenation of primary or secondary alkylamines over nickel, platinum, chromium catalysts or in contact with sulphur, or selenium gives acceptable yields of corresponding azomethines.

Reagent used: Hydride transfer reagents (diazonium fluoroborates, trityl perchlorate)



d) Elimination reaction leading to azomethines:

Thermal and base catalysed elimination of substrates derived by electroplilic attack (halogenations, nitrosation, nitration, sulphonation) at the nitrogen atom of primary and secondary alkylamines.



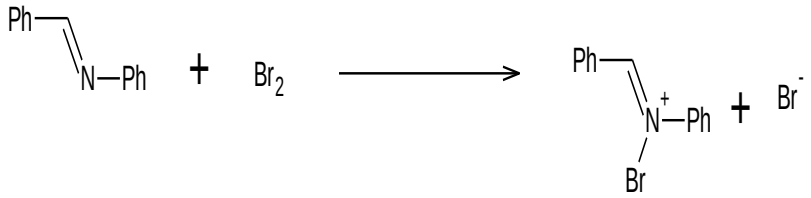
GENERAL REACTIONS OF SCHIFF BASES

a) Reaction with electrophiles

Electropliles attack predominantly at nitrogen atom in the azomethines.

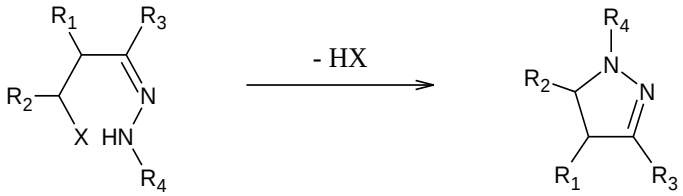
i) Halogenation

Halogens are reported to add in a 1,2-fashion to the carbon-nitrogen double bond in N-arylaldimines. The product of the reaction of benzylidene aniline with bromine in carbon tetrachloride is formulated as an N-bromoiminium bromide.



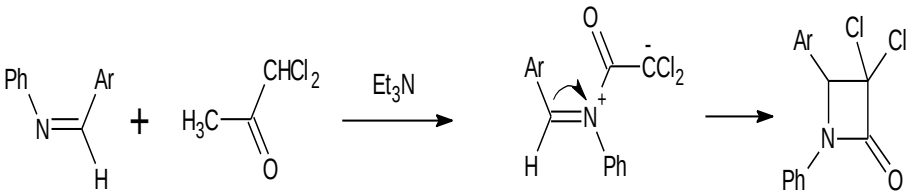
ii) Alkylation

Direct alkylation of N-alkyl aldimines and ketimines occurs at the nitrogen atom to give corresponding iminimum salt. N-alkylation of N-monosubstituted hydrazones has been applied intramolecularly providing a general route to pyrazolines.



iii) Acylation:

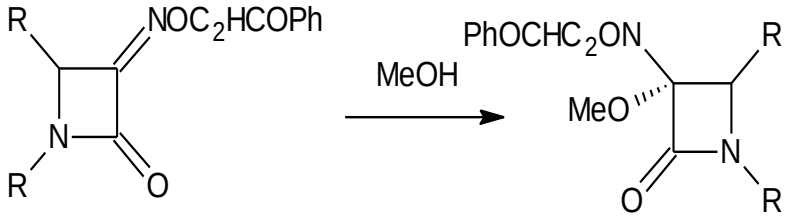
Acylation of Schiff's base by acid anhydrides, acid chlorides and acyl cyanides is initated by attack at the nitrogen atom and leads to net addition of acylating agent to the carbon nitrogen double bond.



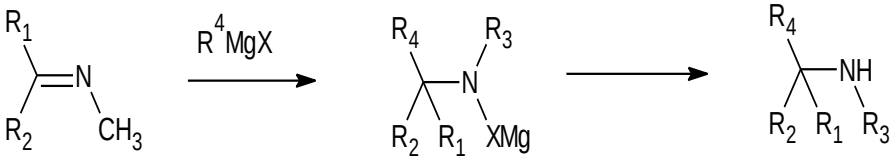
b) Reaction with nucleophiles

Nucleophilic reagents attack azomethines at imidyl carbon atom.

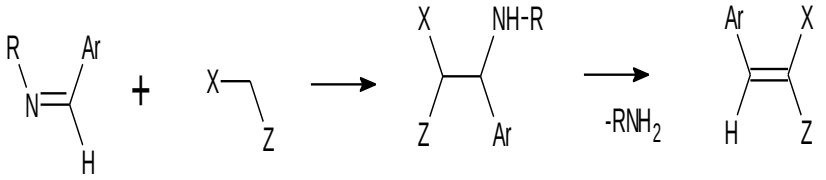
1) Alkoxide adds to Schiff's base giving corresponding α- alkoxyamino compounds.



2) Reaction with Grignard reagents: Schiff base lacking hydrogen atoms α to the carbon nitrogen double bond react with Grignard reagents to give adducts which on hydrolytic workup afford secondary amine in excellent yield.

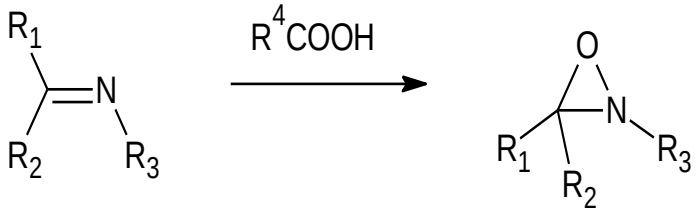


3) Reaction with active methylene compounds: Schiff base react readily with active methylene compounds to give adducts which tend to eliminate the elements of an amine affording the corresponding alkene.



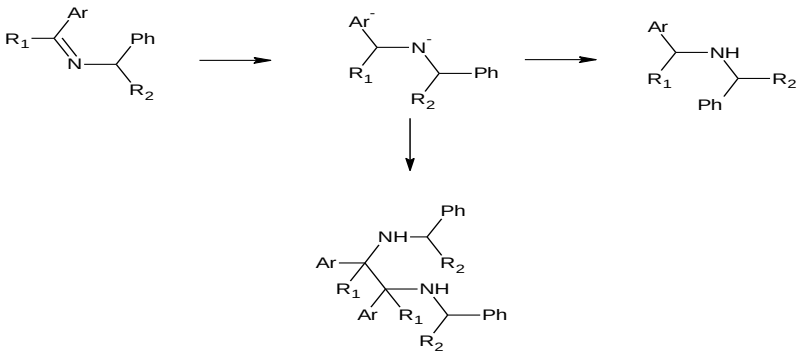
c) Oxidation

Oxidation of Schiff base with a peroxy acid results in cleavage of carbon nitrogen bond to give a carbonyl compound and a nitroso compound. On the other hand oxidation using peroxy acid at low temperature (0^0 C) affords an excellent synthetic route to oxaziridines.



d) Reduction

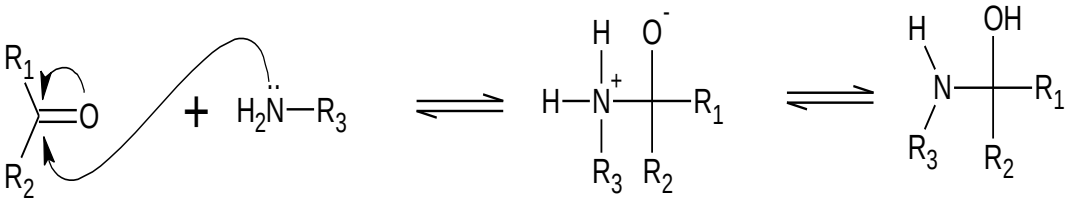
Alkali metals in inert solvents such as ether or toluene tend to promote reductive dimerization by a radical coupling mechanism to afford diamino compound as a major product.Metal proton reagents (sodium, sodium amalgam, magnesium, aluminium in ethanol etc.) smoothly reduce Schiff base to corresponding amines.



MECHANISM

Imines are prepared by a reaction between a carbonyl compound and a primary amine. If the imine contains a hydrogen atom, it is unstable and usually cannot be isolated. However when the imine contains aromatic group on the nitrogen, the resulting imine is stable and can be isolated. The products are called Schiff base.

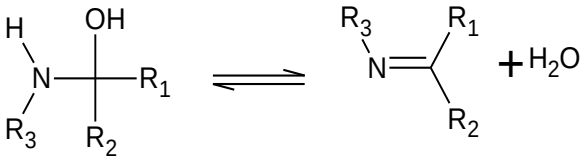
Step 1:



Nucleophilic addition of the amine to the carbonyl compound followed by transfer of a proton from nitrogen to oxygen leads to the formation of tetrahedral carbinolamine intermediate.

Step 2:

Elimination of water to gives the corresponding azomethines.



MATERIALS AND METHODS

Reagents and chemicals used:

Aniline derivatives(aniline,4-chloroaniline,4-bromo aniline, 4-methoxyaniline, 3-methoxy aniline, 4-nitroaniline ,3-nitroaniline,4-methylaniline, Phosphorous oxychloride, Dimethyl formamide, isoniazid,glacial acetic acid, Zn dust,methanol, 70%acetic acid

All the reagents and chemicals were procured from Sigma Aldrich High media and Lobachem. All the compounds procured were purified and dried, whenever necessary before use, following standard methods.

Apparatus used:

Beakers, test tubes, glass rods, magnetic stirrer, thermometer, round bottom flask, reflux condenser, iodine flasks, watch glass, conical flasks, burette and pipettes.

Analytical work:

- Melting point was determined by using melting point apparatus MR-VIS, visual melting range apparatus, LABINDIA and uncorrected.
- Reactions were monitored by thin layer chromatography (TLC) on a pre-coated silica gel G plated using Iodine vapor as visualizing agent.
- UV spectra were recorded on JASCO V-530 UV-VIS spectrometer in the department of Pharmaceutical analysis, College of Pharmacy, SRIPMS, Coimbatore.
- IR spectra were recorded on JASCO FTIR-420 series in the department of Pharmaceutical Analysis, College of Pharmacy, SRIPMS, Coimbatore.
- NMR spectra were recorded on Bruker AVANCE III 500MHz NMR spectrometer at KAMARAJ UNIVERSITY MADURAI.
- Mass spectra were recorded on JEOL GCMATE II GC-MS spectrometer at SAIF, VIT VELLORE.

METHODOLOGY

Step 1:Synthesis of acetanilides

(Aniline, 4-bromoaniline, 4-chloroaniline, 3-methoxyaniline, 4-methoxyaniline,3-nitroaniline, 4-nitroaniline, 4-methylaniline were converted into their corresponding acetanilides)

A mixture of aniline and substituted anilines 0.11mol and Zn dust were added to acetic acid(30ml) in a 100ml round bottom flask, and heated over a gentle flame using water condenser. Heating was continued for about 2hrs.The reaction mixture was then carefully poured in cold water(100ml) in 250ml beaker with cooling and vigorous stirring. The shining crystals of their corresponding acetanilides were separated slowly. After 15mins the corresponding acetanilide crystals were collected by filtration. The solid crystals were washed over Buchner funnel with water and product was dried (yield 10g). It was crystallized in boiling water (if necessary charcoal may be used).

Acetanilide-90%yield,3-Methoxy acetanilide-95yield, 4-Methoxy acetanilide 90%yield, 4-chloroacetanilide-90%yield,4-bromoacetanilide-90% yield ,4-methyl acetanilide-80% yield,3-nitroacetanilide 50% yield, 4-nitroacetanilide 60% yield

Step 2: Synthesis of 2-chloro-3-formyl quinolines [1]

The compounds were prepared from acetanilide and corresponding substituted acetanilides under Vilsmeier - Haack reagent ($POCl_3$/DMF).

To a solution of acetanilide and corresponding substituted acetanilides (5 mmol) in dry DMF (15mmol) at 0-5^{o}C with stirring $POCl_3$ (60mmol) was added dropwise. The reaction mixture was stirred at 80-90^{o}C for time ranging between 4-16hr. This mixture was poured in crushed ice, stirred for 5 mins where corresponding 2-chloro-3-formyl quinolines formed was filtered, washed well with water and dried. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile.

2-chloro-3-formyl quinoline-70% yield,6-bromo- 2-chloro-3-formyl quinoline -80% yield,6-chloro 2-chloro-3-formyl quinolone-80% yield,7-methoxy-2-chloro-3-formyl quinolone-90% yield, 6-methoxy-2-chloro-3-formyl quinolone-90% yield,7-nitro-2-chloro-3-formyl quinolone-40% yield ,6-nitro-2-chloro-3-formyl quinolone-60% yield ,4-methyl-2-chloro-3-formyl quinolone-60% yield.

Step 3: Synthesis of 3-formyl 2(H)quinolones:[1]

A suspension of 2-chloro-3-formyl quinoline and substituted 2-chloro-3-formyl quinolines (1mmol) was dissolved in 70% CH_3COOH(10ml) and heated under reflux for 4-6hrs.The completion of reaction was checked by TLC.Upon cooling the reaction mixture, corresponding 3-formyl-2- quinolones formed were precipitated, filtered, washed well with water, dried and purified by recrystallization from DMF.

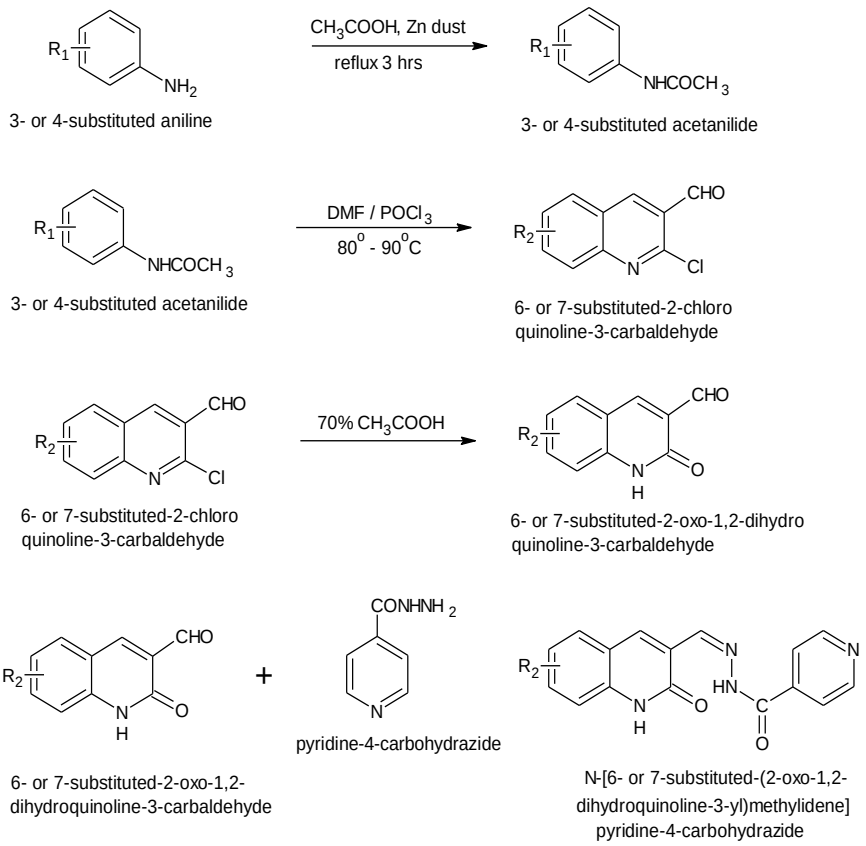
3-formyl-2-quinolones-70%,6-bromo-3formyl-2-quinolones -80% yield, 6-bromo-3formyl-2-quinolones -80% yield,6-chloro-3formyl-2-quinolones -80% yield,7-methoxy-3formyl-2-quinolones -80% yield,6-methoxy-3formyl-2-quinolones -80% yield,7-nitro-3formyl-2-quinolones -60% yield,6-nitro-3formyl-2-quinolones -60% yield, 6-methyl-3formyl-2-quinolones -80% yield.

Step 4: Synthesis of Schiff base from 3-formyl-2-quinolones [33]

Equimolar quantities of 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones (0.01mol) and isoniazid(0.01mol) was dissolved in ethanol and 2-4 drops conc.sulphuric acid was added and refluxed for 2-4hrs. It was then cooled and poured into crushed ice. Schiff bases of corresponding 3-formyl-2-quinolones thus obtained were filtered, washed with water and recrystallised from ethanol.

3-formyl-2-quinolone Schiff base -77% yield,6-bromo- 3-formyl-2-quinolone Schiff base -80% yield, 6-chloro- 3-formyl-2-quinolone Schiff base -90% yield,7-methoxy- 3-formyl-2-quinolone Schiff base -90% yield,6-methyl- 3-formyl-2-quinolone Schiff base -85% yield, 7-nitro- 3-formyl-2-quinolone Schiff base -50% yield, 6-nitro- 3-formyl-2-quinolone Schiff base -60% yield, 6-methyl-3-formyl-2-quinolone Schiff base -85% yield,

SCHEME



R_1	R_2
H	H
4-Br	6-Br
4-Cl	6-Cl
3-OCH_3	7-OCH_3
4-OCH_3	6-OCH_3
3-NO_2	7-NO_2
4-NO_2	6-NO_2
4-CH_3	6-CH_3

PHYSICAL DATA CHARACTERIZATION

C.C	R_1	R_2	MOLECULAR FORMULA	MOLECULAR WEIGHT	MP	RF VALUE	%YIELD
5a	H	H	$C_{16}H12N_4O_2$	292.2902	140.6	0.48	77
5b	4-Br	6-Br	$C_{16}H_{11}N_4O_2Br$	371.188	148.9	0.7	80
5c	4-Cl	6-Cl	$C_{16}H_{11}N_4O_2Cl$	326.7371	154.2	0.76	90
5d	3-OCH_3	7-OCH_3	$C_{17}H_{14}N_4O_3$	322.3181	85.8	0.40	90
5e	4 -OCH_3	6-OCH_3	$C_{17}H_{14}N_4O_3$	322.3181	89.4	0.42	85
5f	3-NO_2	7-NO_2	$C_{16}H_{11}N_5O_4$	337.2902	119	0.74	50
5g	4-NO_2	6-NO_2	$C_{16}H_{11}N_5O_4$	337.2902	123	0.75	60
5h	4-CH_3	6-CH_3	$C_{17}H_{14}N_4O_2$	306.3187	145.2	0.52	85

RECRYSTALLIZATION SOLVENT: ETHANOL

SOLVENT SYSTEM USED: DIOXAN:ETHYLACETATE:WATER(9:1:1)

VISUALIZING AGENT: IODINE VAPOUR

ANTIMICROBIAL STUDIES [74,75]

Apparatus and chemicals required

Sterile swab	:	Hi Media
Non-absorbent cotton	:	Rama Raju Surgical cotton Ltd.
Conical flask	:	Borosil
Test tubes	:	Borosil
Petri dishes	:	SD Fine-Chem Ltd.
Micropipettes	:	VARI pipettes (Hi-Tab Lab)
Autoclave	:	Universal Autoclave
Laminar Air Flow unit	:	CLEAN AIR Instruments Inc.
Microtips	:	Tarsons

The antibacterial screening was carried out in the Pharmaceutical Biotechnology laboratory, College of Pharmacy, SRIPMS, Coimbatore.

Media used

Nutrient media which is gelled with 2% agar (bacteriological grade) is used as the medium for the antibacterial screening.

The nutrient media contains the following ingredients:-

Nutrient broth	:	13g/l
Agar	:	15.00 g/l
Final pH at 25°C	:	7.4(±0.2)

Media preparation and sterilization

The ingredients were dissolved in distilled water with the aid of heat and the pH was adjusted to 7.4(±0.2) by using dilute acid or alkali.

30-35 ml of nutrient media was transferred to Petri plates and sealed. The media is autoclaved at a pressure of 15 psi (121°C) for not less than 15 minutes.

Microorganisms used

Staphylococcus aureus NCIM 2079, *Bacillus subtilis* NCIM 2063, *Escherichia coli* NCIM 2918 and *Pseudomonas aeruginosa* NCIM 2036 were procured from National Chemical Laboratory, Pune and stored in the Pharmaceutical Biotechnology laboratory, College of Pharmacy, SRIPMS, Coimbatore,Tamil Nadu**.**

- The strains were confirmed for their purity and identified by Gram's staining method and their characteristic biochemical reactions.
- The selected strains were preserved by sub culturing them periodically on nutrient agar slants and storing them under frozen conditions.
- For antimicrobial study, fresh 24 hours broth cultures were used after the standardization of the culture.

Drugs used	:	5a-h(500µg/ml)
Standard drug	:	Ofloxacin (200µg/ml)
Solvent	:	Dimethyl sulfoxide

WORKING CONDITIONS IN LABORATORY

The entire work was done by using horizontal laminar flow hood so as to provide aseptic conditions. Before the commencement of the work, air sampling was carried out using a sterile nutrient agar plate and exposing it to the environment inside the hood.

After incubation, it was checked for the growth of microorganism and absence of growth confirmed aseptic working condition.

STANDARDIZATION OF INOCULUMS

- All organisms were grown overnight (24 hours) at 37°C on nutrient agar and harvested during the stationary growth phase.
- Active cultures for experiments were prepared by transferring a loopful of cells from the stock culture to the test tubes containing nutrient media, incubated for 24 hours at 37°C.
- Inoculum was standardized by matching the turbidity of the culture to 0.5 McFarland standard. The standard was produced by mixing 0.05 ml of 0.048 $BaCl_2$ (1.175%w/v bariumchloridedehydrates) with 99.5 ml of 0.36N H_2SO_4.
- If the turbidity of the culture matches that of the McFarland standard, the culture inoculating suspension has approximately 2.0×10.6CFU/ml of bacteria.

ANTI- BACTERIAL SCREENING BY KIRBY-BAUER METHOD

- Nutrient media plates were prepared aseptically to get a thickness of 5-6mm. The plates were allowed to solidify and inverted to prevent condensate falling on the agar surface. The plates were dried at 37°C before inoculation. The organisms were inoculated as per the following method in the plates prepared earlier.
- The sterile swab was dipped in the previously standardized inoculum and excess of inoculums was removed by pressing and rotating the swab firmly against the sides of the culture tube above level of liquid. The swab was streaked all over the surface of the medium three times, rotating the plates through an angle of 60°C after each application.
- Finally the swab was pressed round the edges of the agar surface.
- The inoculation medium was allowed to dry at room temperature, with the lid closed.

- The drug was poured in the wells, which are made with the help of a borer. And the measured quantity of the drug is poured with the help of the micro-pipette. Nearly 50µl of the solution is poured into the wells. The plates were kept in the refrigerator for 1 hour to facilitate the diffusion of the drugs.
- Plates were prepared in triplicate and they were then incubated for 18-24 hours at 37°C.
- After the incubation, the diameter of the zone of inhibition around the drugs were measured and compared with that of the standard.
- All the synthesized compounds were tested for antibacterial activity against Gram positive and Gram negative bacteria.
- Saturated solutions of the compounds were first studied and the compounds with zones of inhibition greater than 15mm were taken for quantitative studies.

Screening of newly synthesized compound for antibacterial activity against gram-positive bacteria

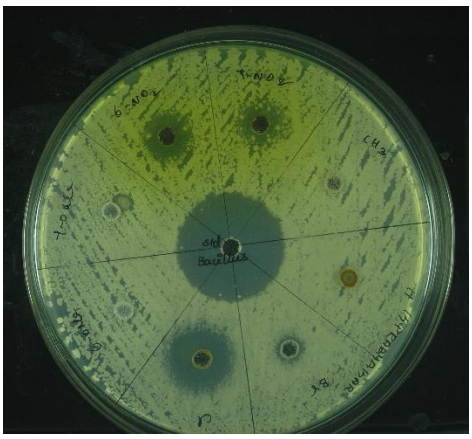
Test drug	: Synthesized compounds 5a-h (500 µg/ml)
Standard drug	: Ofloxacin 200µg/ml
Solvent used	: Dimethyl sulfoxide
Blank solution	: Dimethyl sulfoxide

ANTIBACTERIAL ACTIVITY AGAINST GRAM-POSITIVE BACTERIA

COMPOUND CODE	DIAMETER OF ZONE INHIBITION(mm)	
	Staphylococcus aureus **NCIM 2079**	**Bacillus subtilus NCIM 2063,**
5a	-	-
5b	-	11
5c	17	22
5d	-	-
5e	-	-
5f	-	18
5g	-	16
5h	-	-
Control	-	-
std ofloxacin	32	39

(-)indicates no zone of inhibition

Staphylococcus aureus **NCIM 2079**



Bacillus subtilus NCIM 2063

Screening of newly synthesized compound for antibacterial activity against gram-negative bacteria

Test drug : Synthesized compounds 5a-h (500 µg/ml)

Standard drug : Ofloxacin 200µg/ml

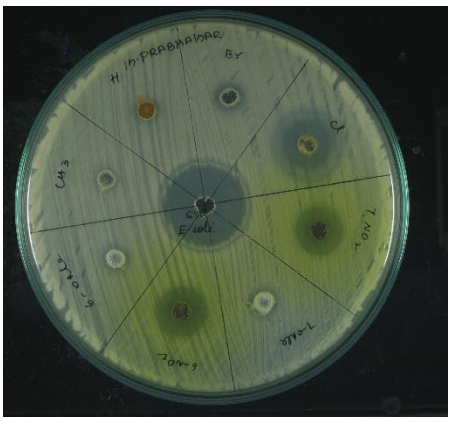
Solvent used : Dimethyl sulfoxide

Blank solution : Dimethyl sulfoxide

ANTIBACTERIAL ACTIVITY AGAINST GRAM-NEGATIVE BACTERIA

COMPOUND CODE	DIAMETER OF ZONE INHIBITION(mm)	
	***Escherichia coli* NCIM 2918**	***Pseudomonas aeruginosa* NCIM 2036**
5a	-	-
5b	13	-
5c	19	24
5d	-	-
5e	-	-
5f	19	18
5g	18	18
5h	12	-
Control	-	-
Std ofloxacin	32	32

(-) indicates no zone of inhibition



Escherichia coli
NCIM 2918

Pseudomonas aeruginosa
NCIM 2036

SCREENING FOR ANTI-FUNGAL Activity [78]

MYGP MEDIA FOR CANDIDA ALBICANS

Ingredients

Malt extract powder : 3g/l

Yeast extract powder : 3g/l

Dextrose : 10g/l

Agar : 15g/l

Water to make : 100ml

Final pH at 25^{o}c : 5.4±0.2

POTATO DEXTROSE AGAR FOR ASPERGILLUS NIGER

Ingredients

Potato dextrose agar : 39g/l

Water to make : 1000ml

Preparation

The ingredients were dissolved in 1000ml of distilled water and boiled to dissolve the medium completely.

Sterilization

15-30ml of MYGP MEDIA and Potato dextrose agar was transferred to petri plates and sealed. It was then autoclaved at pressure of 15psi (121˚c) for not less than 15mins.

Organism used

Candida albicans NCIM 3100 and Aspergillus niger NCIM 596

Drugs used : synthesized drugs 5a-h(500mg/ml)

Standard drugs : fluconazole (200µg/ml)

Solvent : Dimethyl sulfoxide

ANTI-FUNGAL SCREENING BY KIRBY-BAUER METHOD

- **MYGP MEDIA** and **POTATO DEXTROSE AGAR** plates were prepared aseptically to get a thickness of 5-6mm. The plates were allowed to solidify and inverted to prevent condensate falling on the agar surface. The plates were dried at 37°C before inoculation.
- The organisms (Candida albicansNCIM3100 and Aspergillus niger NCIM596) were inoculated as per the following method in the plates prepared earlier, by dipping a sterile swab in the previous standardized inculums was removed by pressing and rotating the swab firmly against the sides of the culture tube above the level of liquid and finally streaking the swab all over the surface of the medium three times,rotating the plates through an angle of 60˚after each application.
- Finally the swab was pressed around the edges of agar surface.It was allowed to dry at room temperature, with the lid closed.
- The sterile disc containing test drugs,standard and blank were placed on the previously inoculated surface of MYGP MEDIA and POTATO DEXTROSE AGAR plates.The plates were kept in the refrigerator for 1 hour to facilitate the diffusion of th drugs.
- Plates were prepared in triplicate and they were incubated for 18-24hours at 37˚c.
- After the incubation ,the diameter of the zone of inhibition around the drugs were measured and compared with that of standard.
- All the synthesized compounds were tested for antifungal activity against Candida albians and Aspergillus niger.

- Saturated solutions of compounds were studied and the compounds with zone of inhibition greater than 15mm were taken for quantitative studies.

Screening of newly synthesized compound for antibacterial activity against gram-positive bacteria

Test drug : Synthesized compounds 5a-h (500 µg/ml)

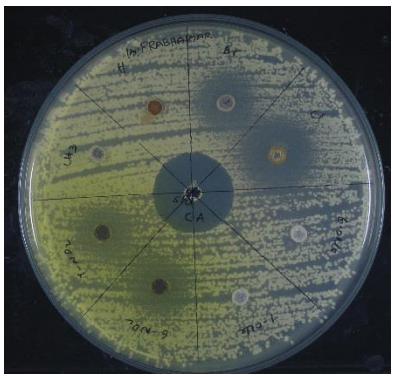
Standard drug : Flucanazole 200µg/ml

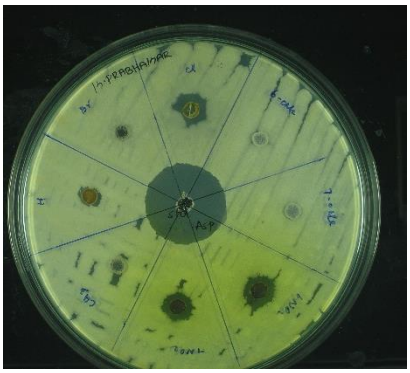
Solvent used : Dimethyl sulfoxide

Blank solution : Dimethyl sulfoxide

COMPOUND CODE	Diameter of zone of inhibition(mm)	
	Candida albicans NCIM3102	Aspergillus niger NCIM596
5a	-	-
5b	**23**	-
5c	**27**	**14**
5d	-	-
5g	-	-
5f	**22**	**22**
5g	**20**	**15**
5h	-	-
Control	-	-
Std fluconazole	**30**	**32**

(-)indicates no zone of inhibition





Candida albicans NCIM3102 **Aspergillus niger NCIM596**

ANTIMYCOBACTERIAL STUDIES:

Conventional agar diffusion technique for susceptibility tests, which rely on the size of zone of inhibition surrounding a drug containing disc are not suitable for the slowly growing Mycobacterium species because the drug diffuses throughout the medium before the organism has the chance to grow. So, the following principles are recognized for the antimycobacterial screening.

- The composition of medium should have a minimal effect on drug inactivation. So, Middle Brook 7H9 broth base is used.
- Drug containing medium should be stored in a refrigerator shielded from light and kept in plastic tubes tightly closed in order to protect them from evaporation.
- Homogenization of inoculum is essential to eliminate large clumps of cells.

SUSCEPTIBILITY TESTING

This is done by two methods:

- Direct method
- Indirect method

Direct method

This was done if acid-fast bacilli are seen on the smear of the concentrated clinical specimen. Dilutions are made and inoculated.

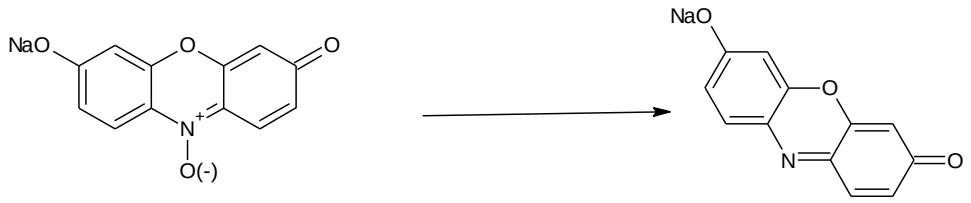
Indirect method

In this method, bacterial mass is suspended in Middle Brook 7H9 broth containing these or four small sterile glass beads. Mixture is placed on a vortex mixer and precautions are taken to prevent aerosol production. Tube is allowed to stand for 15 min. The stock suspensions are diluted and 0.1 ml is inoculated into control and drug containing media.

The antimycobacterial screening was carried out in Maratha Mandal NGH Institute of Dental Sciences and Research Center, Belgaum,Karnataka

ANTITUBERCULAR SCREENING BY MICROPLATE ALAMAR BLUE ASSAY (MABA)[79]

Alamar Blue is a cell viability assay reagent which contains the cell permeable, non-toxic and weakly fluorescent blue indicator dye called resazurin. It is an oxidation-reduction indicator used for the screening of cell growth, particularly in various cell toxicity studies. The dye changes its colour from blue to pink and becomes fluorescent, when reduced to resorufin by oxidoreductases within viable cells



resazurin(oxidised) resorufin(reduced)

Alamar Blue is used for the screening of antitubercular activity. Since Mycobacterium is an aerobic organism, its presence of growth turns Alamar Blue to pink colour. Hence, pink colour indicates the presence of growth (no antitubercular activity) and blue colour indicates the absence of growth (inhibitory activity of agents tested).

Procedure

1) The antimycobacterial activity of compounds were assessed against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA).

2) This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. To the outer perimeter of sterile 96 wells plates, 200µl of sterile deionized

water was added to minimize evaporation of medium in the test wells during incubation.

4) The 96 wells plates received 100 µl of the Middlebrook 7H9 broth (inoculated with *Mycobacterium tuberculosis* of H37RV Strain) and serial dilution of compounds were made directly on plate.

5) The final drug concentrations tested were 100 to 0.2 µg/ml.

6) Plates were covered and sealed with parafilm and incubated at 37ºC for five days.

7) After this time, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs.

8) A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth.

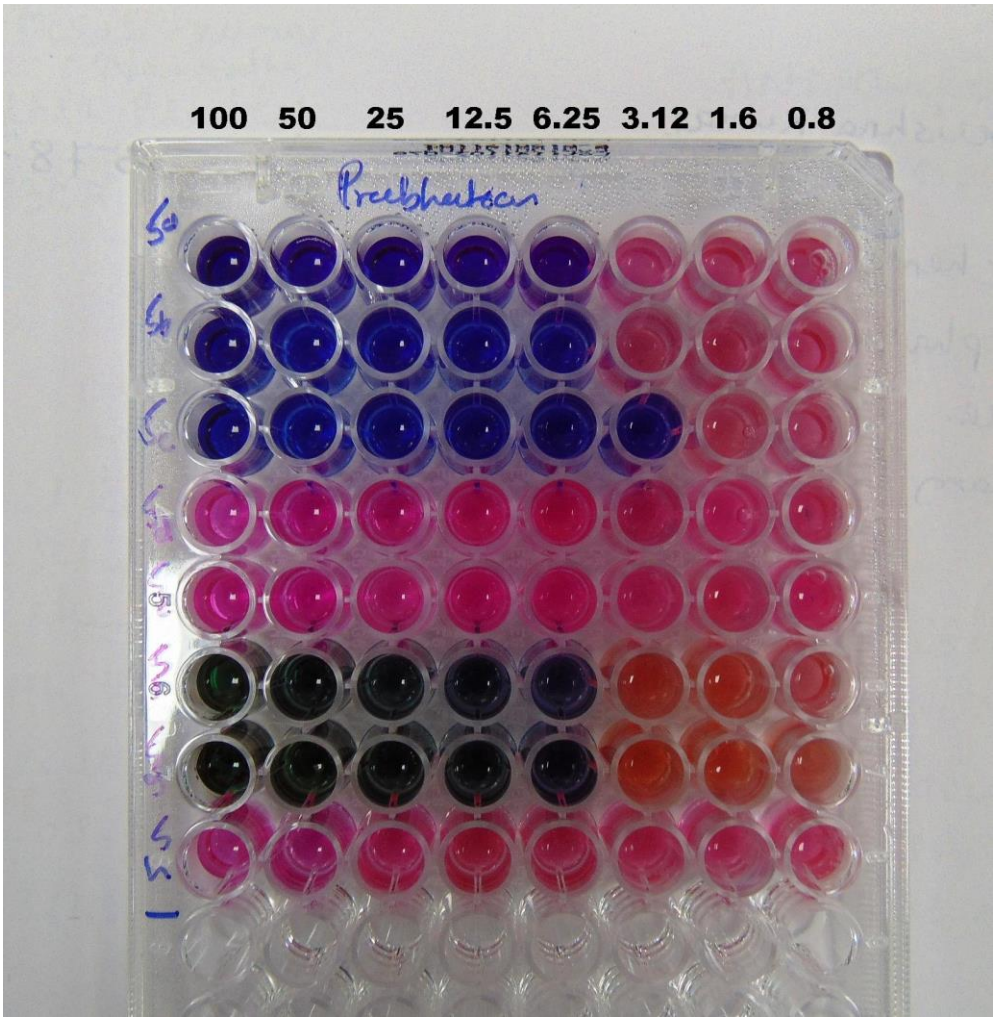
9) The MIC was defined as the lowest drug concentration which prevented the color change from blue to pink.

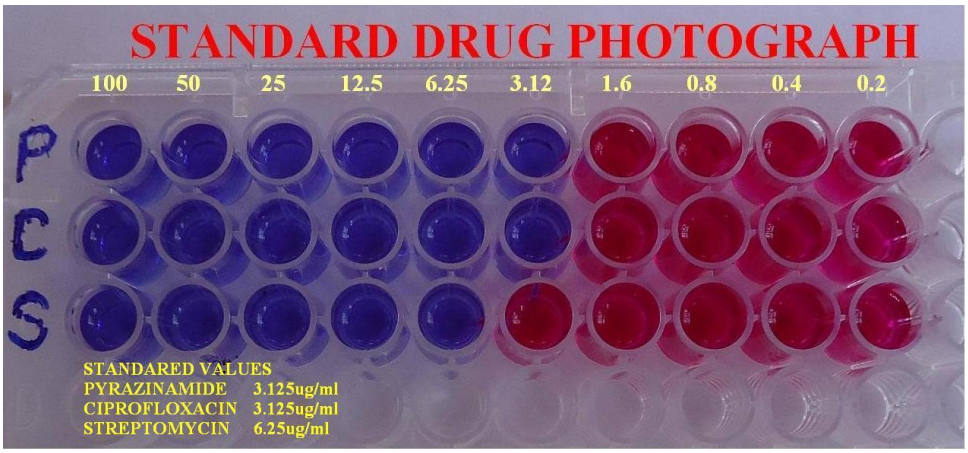
RESULTS AND DISCUSSION

The synthesized compounds were evaluated for *in-vitro* antimycobacterial activity by Alamar Blue assay method and the results are shown in table .

S.NO	COMPOUND CODE	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	5a	S	S	S	S	S	R	R	R
2	5b	S	S	S	S	S	R	R	R
3	5c	S	S	S	S	S	S	R	R
4	5d	R	R	R	R	R	R	R	R
5	5e	R	R	R	R	R	R	R	R
6	5f	S	S	S	S	S	R	R	R
7	5g	S	S	S	S	S	R	R	R
8	5h	R	R	R	R	R	R	R	R
9	Pyrazinamide (std))	S	S	S	S	S	S	R	R
10	Streptomycin (std)	S	S	S	S	S	S	R	R
11	Ciprofloxacin (std)	S	S	S	S	S	R	R	R

S- Sensitive R- Resistant

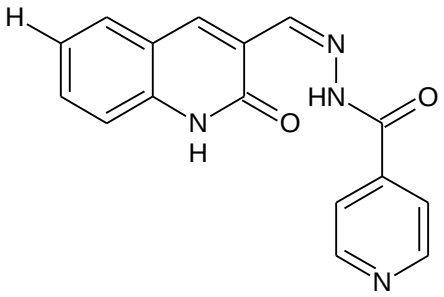

100 50 25 12.5 6.25 3.12 1.6 0.8
Preebhatsan


STANDARD DRUG PHOTOGRAPH
100 50 25 12.5 6.25 3.12 1.6 0.8 0.4 0.2
P
C
S
STANDARED VALUES
PYRAZINAMIDE 3.125ug/ml
CIPROFLOXACIN 3.125ug/ml
STREPTOMYCIN 6.25ug/ml

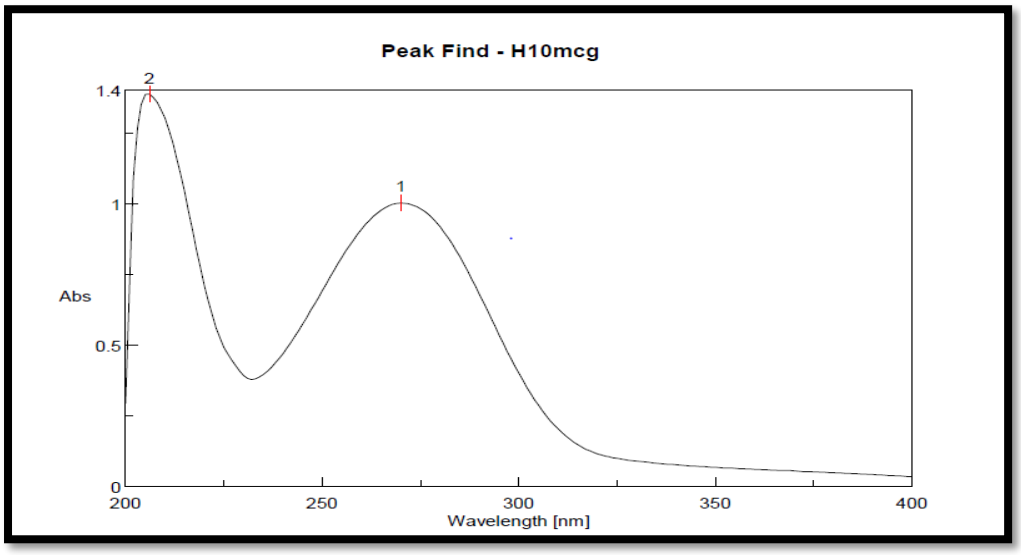
SPECTRAL CHARACTERIZATION DATA [71-73]

The structures of synthesized compounds during the present investigation were established on the basis of chemical d IR, UV, NMR and MASS spectral data. The purity of the compounds were established by single spot on TLC plates.

Compound code-5a



Chemical name	*N*'-[(2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :270nm
IR (KBr,v_{max} in cm^{-1})	C=0 (ketone) -1608,C=O(amido)-1666 C=N -1540 N-N -1009 N-N=C -3312 C-H (AROMATIC) -2937 C=C(aromatic) -1448



[Result of Peak Picking]

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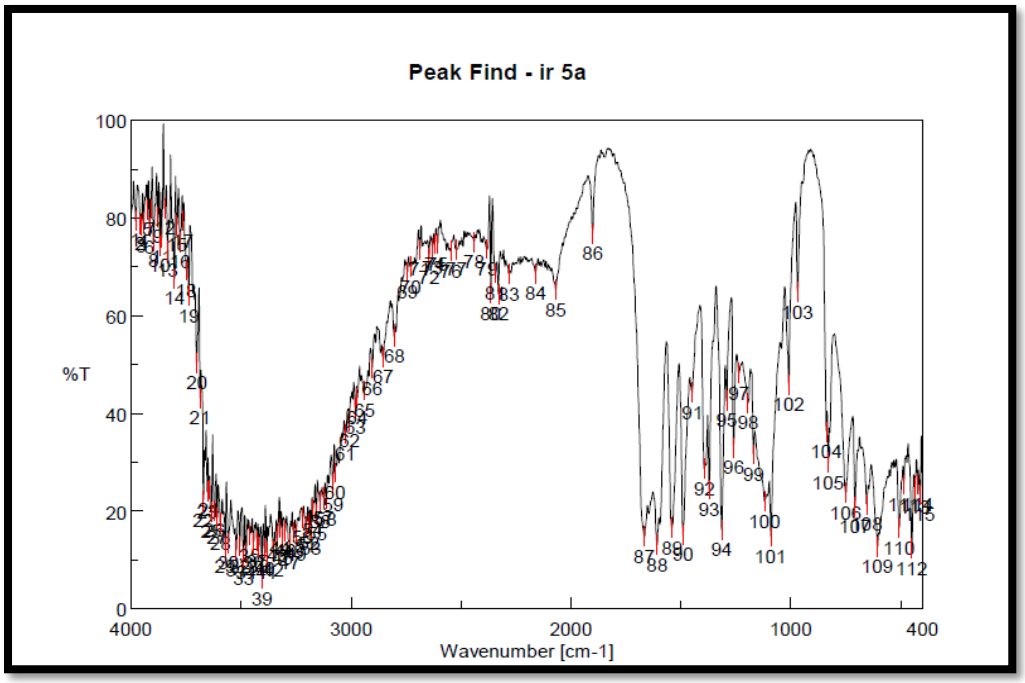

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
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5	3925.39	81.8261	6	3916.72	78.1759
7	3909	81.8791	8	3897.43	75.3654
9	3879.11	80.2318	10	3869.47	74.3557
11	3860.79	76.02	12	3847.29	82.0036
13	3833.79	73.3645	14	3802.94	67.6811
15	3791.37	78.5595	16	3777.87	75.0164
17	3763.4	79.4057	18	3748.94	69.3493
19	3737.37	64.1074	20	3701.69	50.3503
21	3686.26	43.1491	22	3670.84	22.0993
23	3653.48	23.935	24	3646.73	24.4149
25	3636.12	19.8113	26	3620.7	20.1576
27	3608.16	18.6355	28	3594.66	17.5481
29	3572.49	12.6451	30	3558.02	13.3872
31	3521.38	11.9546	32	3504.99	12.8575
33	3488.6	10.3828	34	3477.03	11.424
73	2629.46	73.9215	74	2619.82	74.6724
75	2606.32	74.6614	76	2546.54	73.2391
77	2520.51	73.6032	78	2439.51	75.1672
79	2380.69	73.66	80	2364.3	64.5624
81	2344.05	68.7351	82	2329.59	64.5053
83	2281.38	68.6172	84	2160.85	68.7196
85	2069.25	65.351	86	1901.47	76.8929
87	1666.2	14.7841	88	1608.34	13.1093
89	1540.85	16.5917	90	1489.74	15.1977
91	1448.28	44.26	92	1393.32	28.704
93	1371.14	24.3581	94	1314.25	16.1359
95	1292.07	42.6032	96	1260.25	33.0429
97	1236.15	48.227	98	1193.72	42.1678
99	1169.62	31.6006	100	1118.51	21.9833
101	1090.55	14.7386	102	1009.55	45.8918
103	969.055	64.8357	104	838.883	36.2503
105	829.241	29.9271	106	749.209	23.7634
107	707.747	20.8678	108	654.715	21.4077
109	605.539	12.6675	110	507.187	16.5698
111	485.974	25.4294	112	449.333	12.3774
113	435.834	24.8062	114	422.334	25.4841
115	413.656	23.4378			

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
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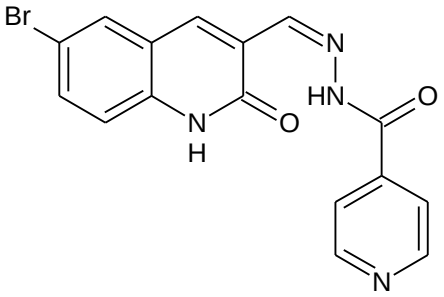
37	3426.89	13.7908	38	3418.21	12.7289
39	3404.71	6.1664	40	3394.1	12.3991
41	3383.5	11.4575	42	3352.64	11.9831
43	3334.32	14.9039	44	3320.82	16.4931
45	3312.14	14.5811	46	3298.64	15.9612
47	3280.32	13.4587	48	3262	15.762
49	3250.43	15.1148	50	3220.54	18.5541
51	3205.11	16.9659	52	3191.61	17.44
53	3182.93	16.3613	54	3173.29	20.3196
55	3157.86	19.4101	56	3140.51	22.001
57	3126.04	22.7839	58	3113.51	22.4549
59	3081.69	25.5057	60	3072.05	27.8292
61	3026.73	35.7628	62	3007.44	38.3869
63	2979.48	41.1355	64	2970.8	43.2088
65	2937.06	44.6929	66	2903.31	49.2967
67	2854.13	51.5389	68	2803.99	55.8154
69	2743.24	68.8814	70	2729.74	70.0874
71	2686.35	73.605	72	2644.89	71.9233

Compound code-5b

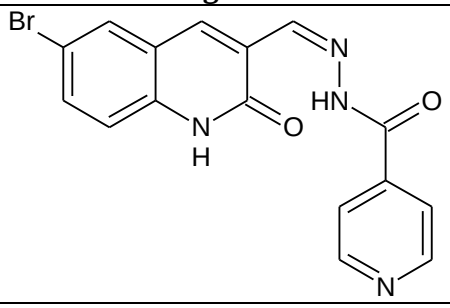
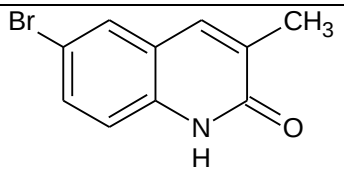
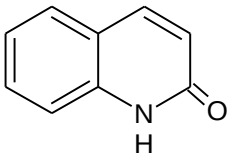
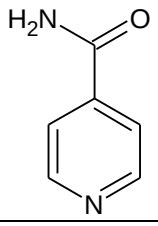


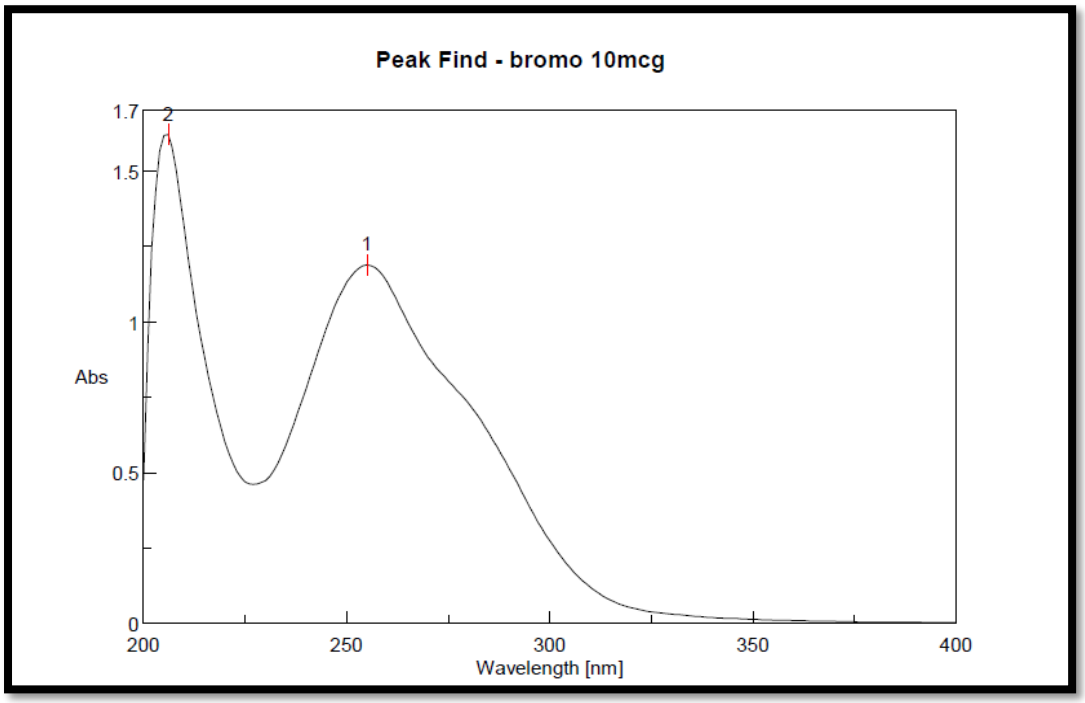
Chemical name	*N*'-[(6-bromo-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :255nm
IR (KBr,v_{max} in cm^{-1})	C=0(ketone) -1671,C=O (amido)-1604 C=N -1536 N-N -1005 N-N=C -3300 C-Br -691 C=C (aromatic)-1488
NMR	^{1}H NMR ^{13}C NMR CH=N -8.55 quinoline- 125 C_5 pyridine -7.61 C=N -148 C_8 quinoline -7.79 pyridine 128

MASS SPECTRAL DATA

Molecular weight of the compound : 372

M+1 peak =373

Sl. No.	Fragments	m/z values
1		372
2		238
3		145
4		122



[Result of Peak Picking]

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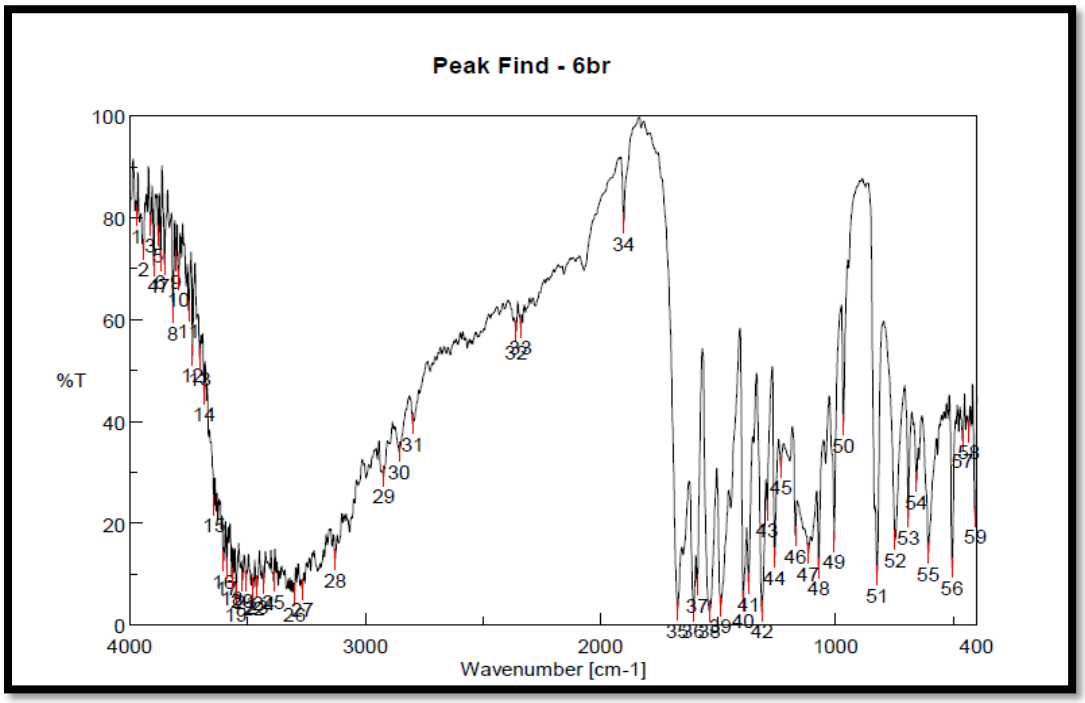
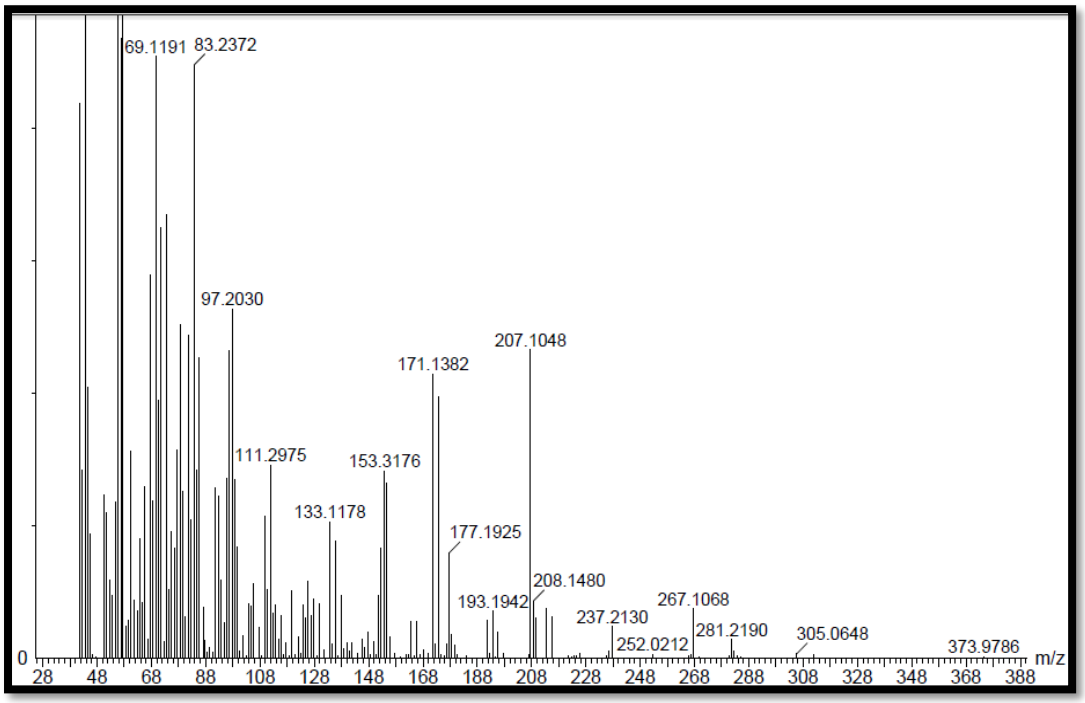
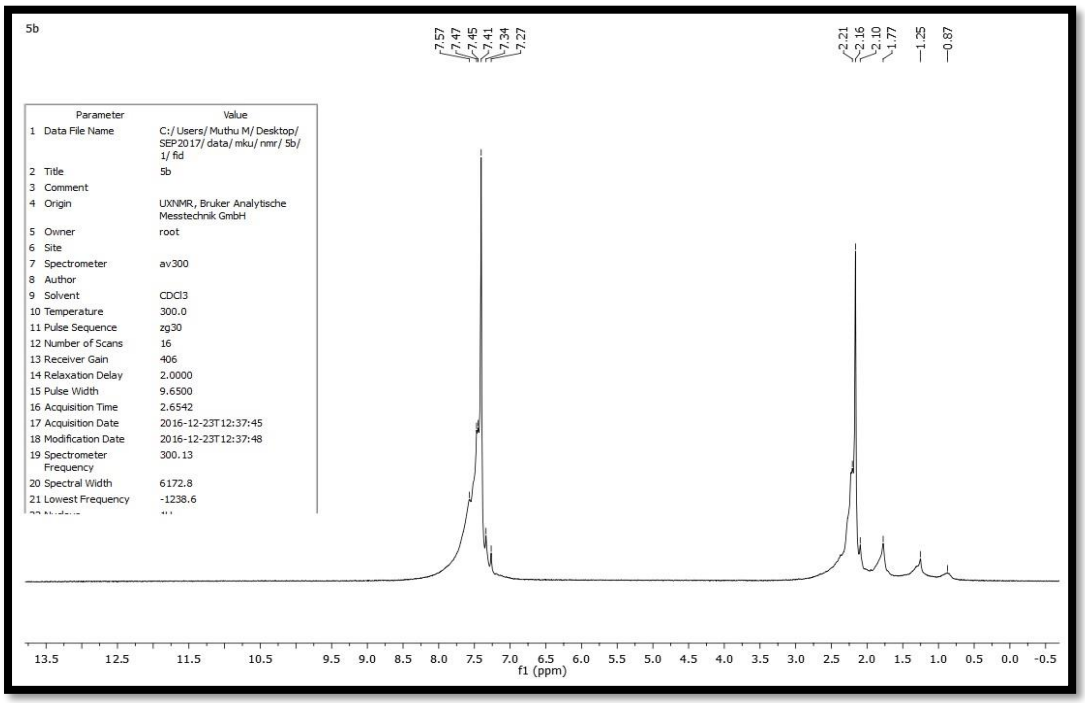


[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3970.71	80.4716	2	3941.79	73.8635
3	3911.9	78.6018	4	3899.36	70.6672
5	3880.08	76.5908	6	3869.47	71.4996
7	3853.08	70.7769	8	3816.44	61.2985
9	3803.9	71.499	10	3793.29	67.9627
11	3749.9	61.7312	12	3734.48	52.9638
13	3702.66	52.2524	14	3685.3	45.3658
15	3642.87	23.5697	16	3601.41	12.5577
17	3587.91	11.145	18	3566.7	9.30593
19	3548.38	6.21196	20	3521.38	8.75967
21	3506.92	8.62848	22	3476.06	7.21251
23	3458.71	7.59784	24	3430.74	8.14095
25	3389.28	8.59121	26	3300.57	5.97741
27	3267.79	6.99921	28	3127.97	12.8393
29	2921.63	29.1809	30	2855.1	34.0394
31	2798.21	39.6497	32	2357.55	57.69
33	2339.23	58.5325	34	1901.47	79.0028
35	1671.98	2.86692	36	1604.48	2.72092
37	1588.09	7.88166	38	1536.02	2.71343
39	1488.78	3.76317	40	1393.32	4.69478
41	1370.18	8.11699	42	1313.29	2.66747
43	1291.11	22.5705	44	1259.29	13.3061
45	1233.25	30.9737	46	1171.54	17.4902
47	1115.62	14.1238	48	1072.23	11.1449
49	1005.7	16.3444	50	966.162	39.3768
51	823.455	9.79353	52	746.317	16.7416
53	691.355	21.2095	54	656.643	28.0926
55	605.539	14.1268	56	504.294	11.2735
57	459.939	36.1709	58	433.905	37.9538
59	405.942	21.3566			

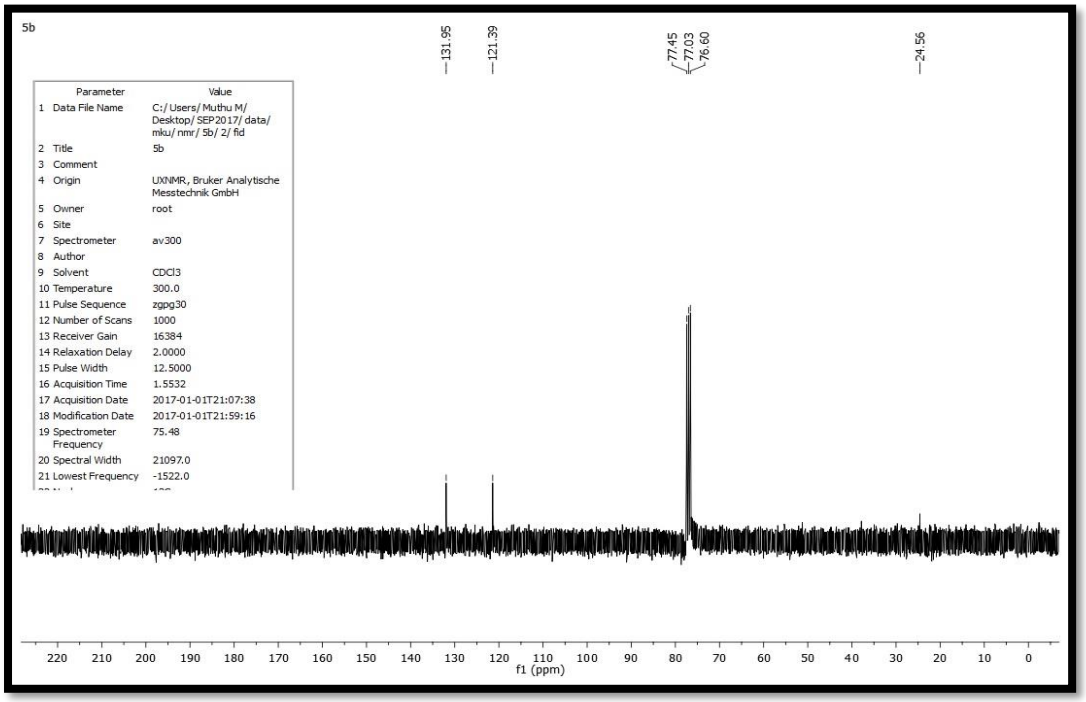


MASS SPECTRA



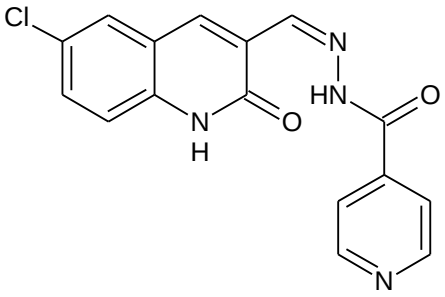
^{1}H NMR

1311

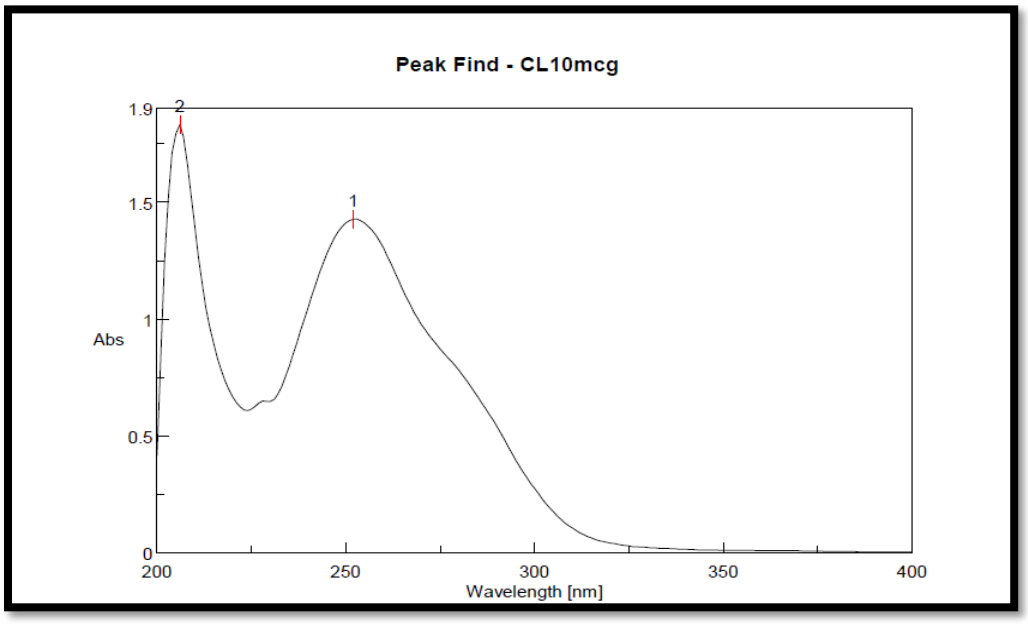


^{13}C NMR

Compound code-5c

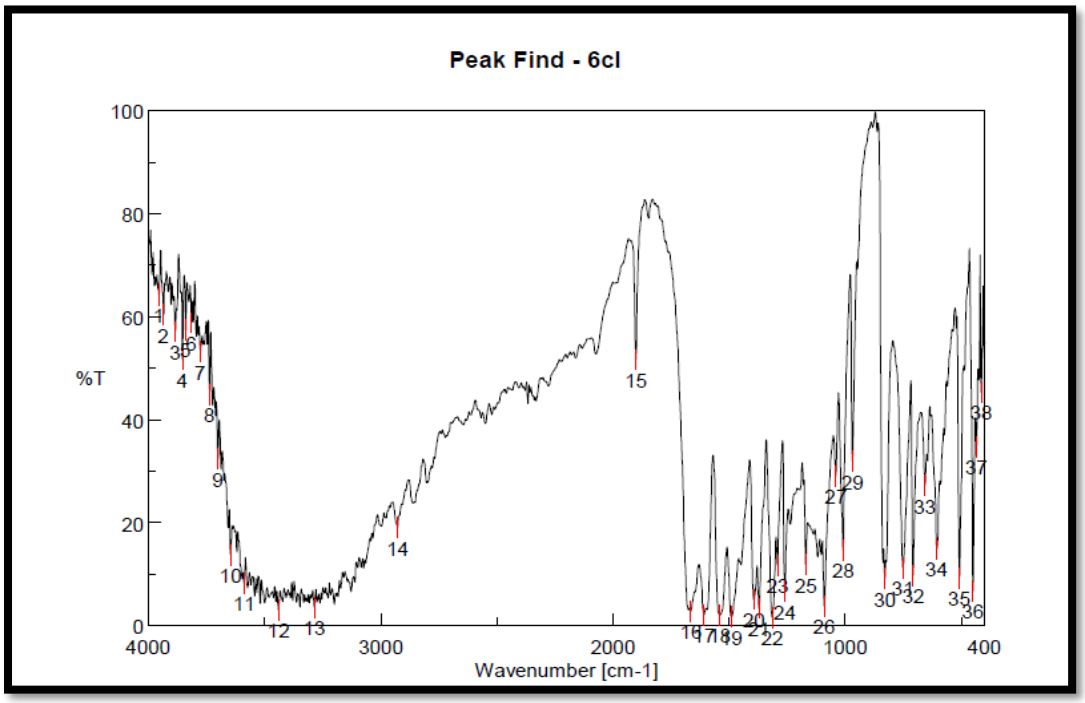


Chemical name	*N*'-[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :252nm
IR (KBr,v_{max} in cm^{-1})	C=0 (ketone) -1664, C=O (amido)-1607 C=N -1540 N-N -1040 N-N=C -3285 C-Cl -751 C=C (aromatic)-1393



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	252	1.42673	2	206	1.83122



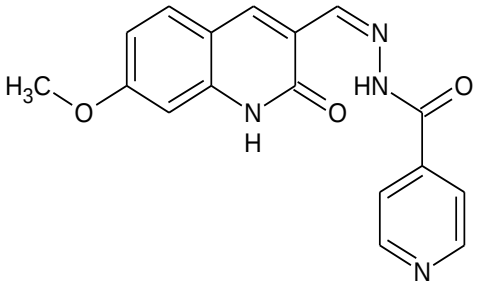
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3954.32	64.19	2	3935.04	60.3486
3	3883.93	57.1315	4	3853.08	51.6356
5	3839.58	57.4766	6	3814.51	58.8108
7	3776.9	53.2311	8	3736.4	44.8695
9	3700.73	32.3845	10	3646.73	13.6486
11	3587.91	8.19642	12	3440.39	3.05024
13	3285.14	3.53758	14	2927.41	18.9768
15	1901.47	51.6592	16	1664.27	2.81549
17	1607.38	2.09308	18	1540.85	1.97428
19	1488.78	1.71973	20	1393.32	5.0471
21	1371.14	3.33343	22	1314.25	1.55775
23	1292.07	11.7671	24	1260.25	6.65332
25	1169.62	11.7881	26	1090.55	3.82085
27	1040.41	29.0015	28	1009.55	14.6468
29	968.09	31.8951	30	829.241	9.11445
31	751.138	11.1965	32	707.747	9.73319
33	656.643	27.2202	34	605.539	14.909

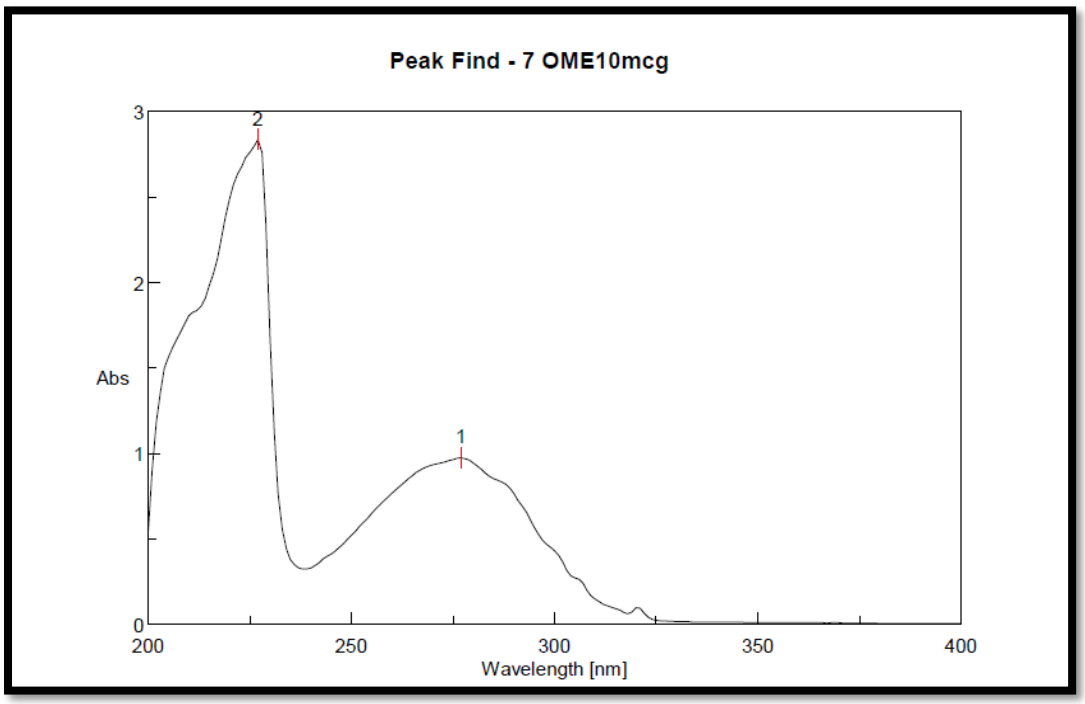
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
35	508.151	9.28913	36	449.333	6.6831
37	434.869	34.7176	38	414.62	45.3465

Compound code-5d

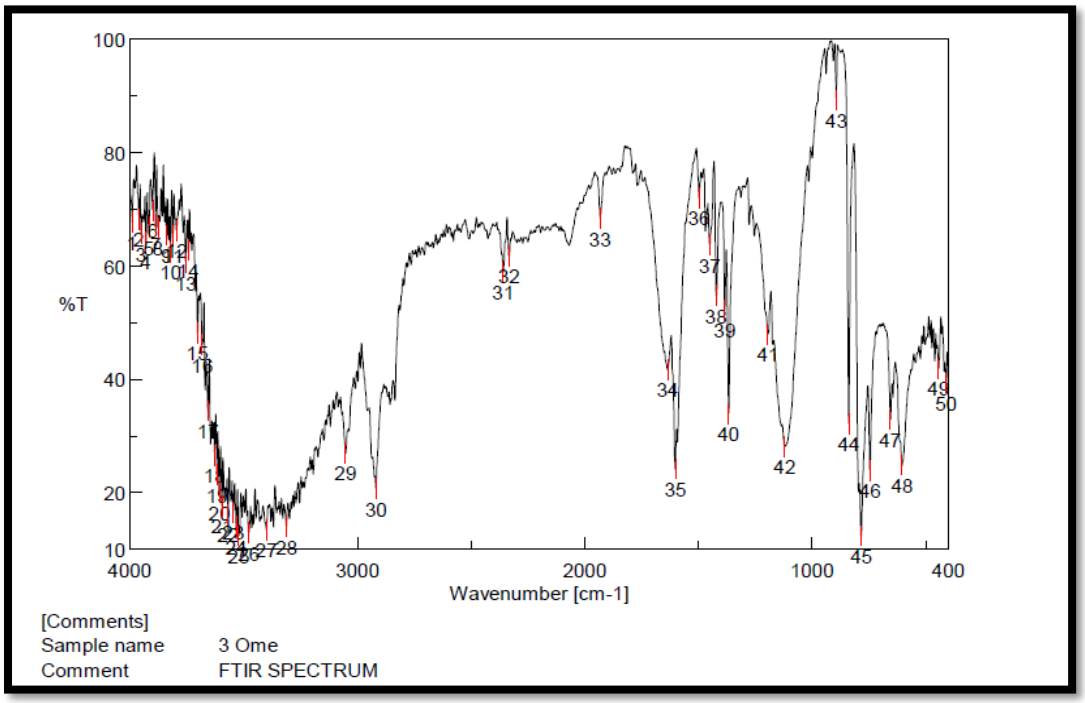


Chemical name	*N*'-[(*Z*)-(7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :277nm
IR (KBr,v_{max} in cm^{-1})	C=0(ketone) -1635, C=O (amido)-1601 C=N -1601 N-N -1141 N-N=C -3312 C-OCH_3 -1121 C=C (ar)-1450



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	277	0.973243	2	227	2.83578



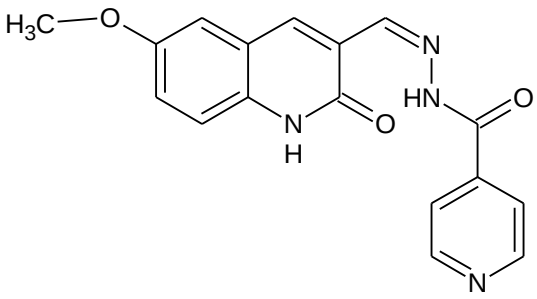
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3990	67.7377	2	3960.11	68.1892
3	3950.46	65.6632	4	3929.25	64.1926
5	3916.72	66.7725	6	3900.32	69.8774
7	3886.83	67.2941	8	3877.18	66.6849
9	3838.61	65.4459	10	3821.26	62.3446
11	3811.61	65.3101	12	3794.26	66.2531
13	3754.73	60.466	14	3743.15	62.8289
15	3702.66	48.1586	16	3681.44	46.0811
17	3657.34	34.3969	18	3627.45	26.5515
19	3617.8	23.1151	20	3607.2	19.9508
21	3596.59	17.6349	22	3568.63	16.072
23	3545.49	16.4287	24	3531.99	13.9883
25	3521.38	12.3697	26	3477.99	12.8382
27	3398.92	13.357	28	3312.14	14.0366
29	3050.83	26.9358	30	2917.77	20.6507
31	2357.55	58.9067	32	2333.45	61.7085
33	1932.32	68.3729	34	1635.34	41.7127

[Result of Peak Picking]

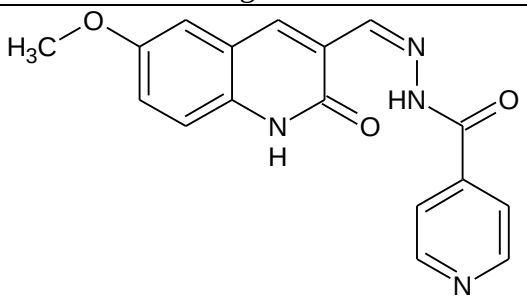
No.	Position	Intensity	No.	Position	Intensity
35	1601.59	24.162	36	1497.45	72.0715
37	1450.21	63.7102	38	1421.28	54.7642
39	1383.68	52.1481	40	1366.32	33.9104
41	1193.72	47.9628	42	1121.4	28.1279
43	893.844	89.273	44	838.883	32.0954
45	783.922	12.3198	46	745.352	23.9259
47	655.679	32.8936	48	604.574	24.7929
49	443.547	41.9016	50	410.763	39.3364

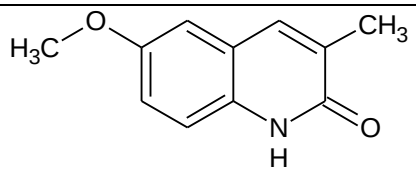
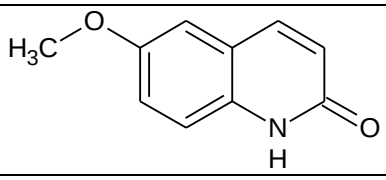
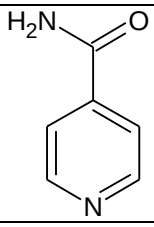
Compound code-5e

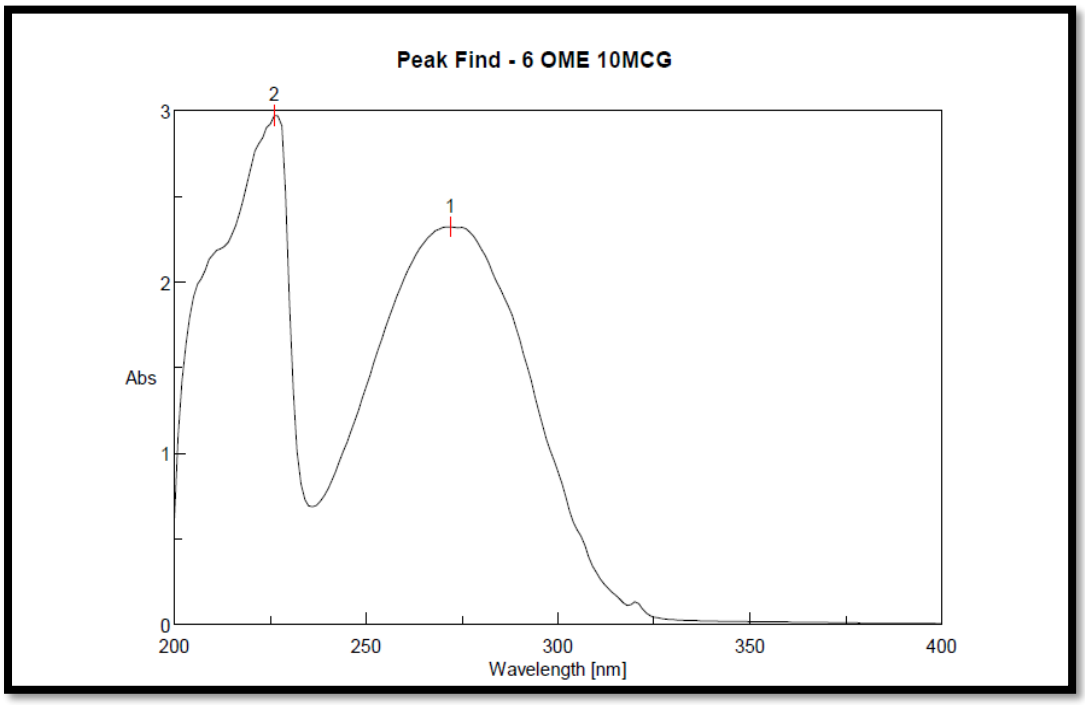


Chemical name	*N*'-[(6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :272nm
IR (KBr,v_{max} in cm^{-1})	C=0(ketone) -1635, C=N -1601 C-N (Ar) -1421 N-N=C -3306 C-OCH_3 -1121 C=C (aromatic)-1449
NMR	^{1}H NMR CH=N -8.55 C_5 pyridine -7.31 C_8 quinoline -7.79 ^{13}C NMR quinoline- 127 C=N -148 pyridine 40

Molecular weight of the compound : 372

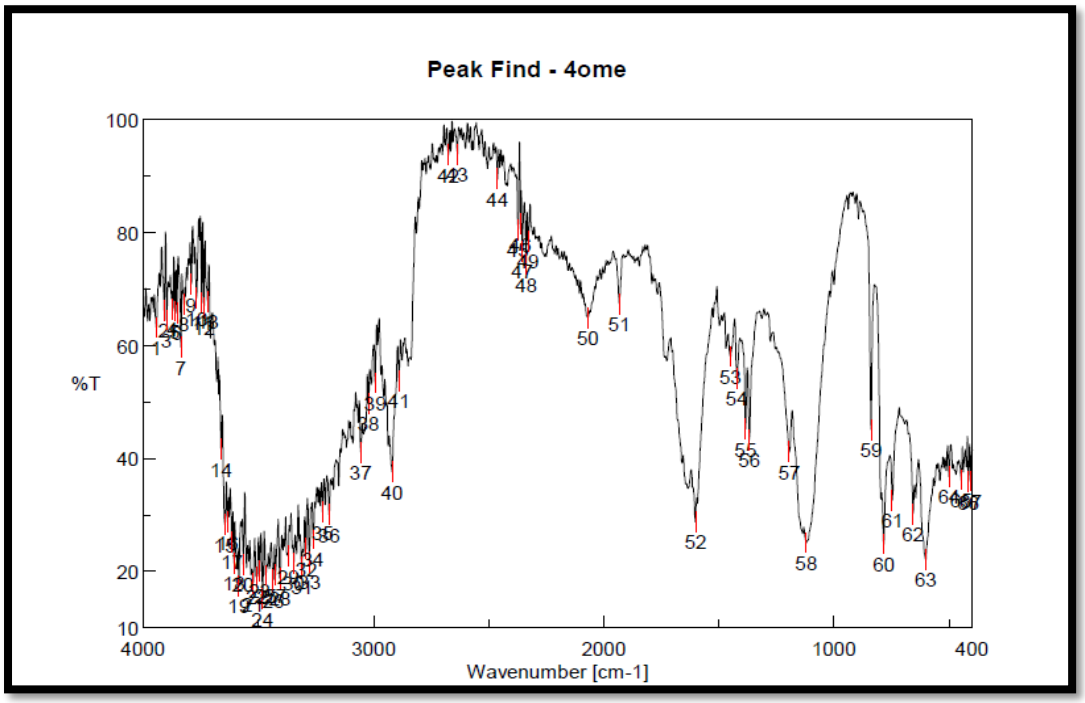
S.No	Fragments	M/z values
1		322

2		189
3		175
4		122



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	272	2.32218	2	226	2.97306



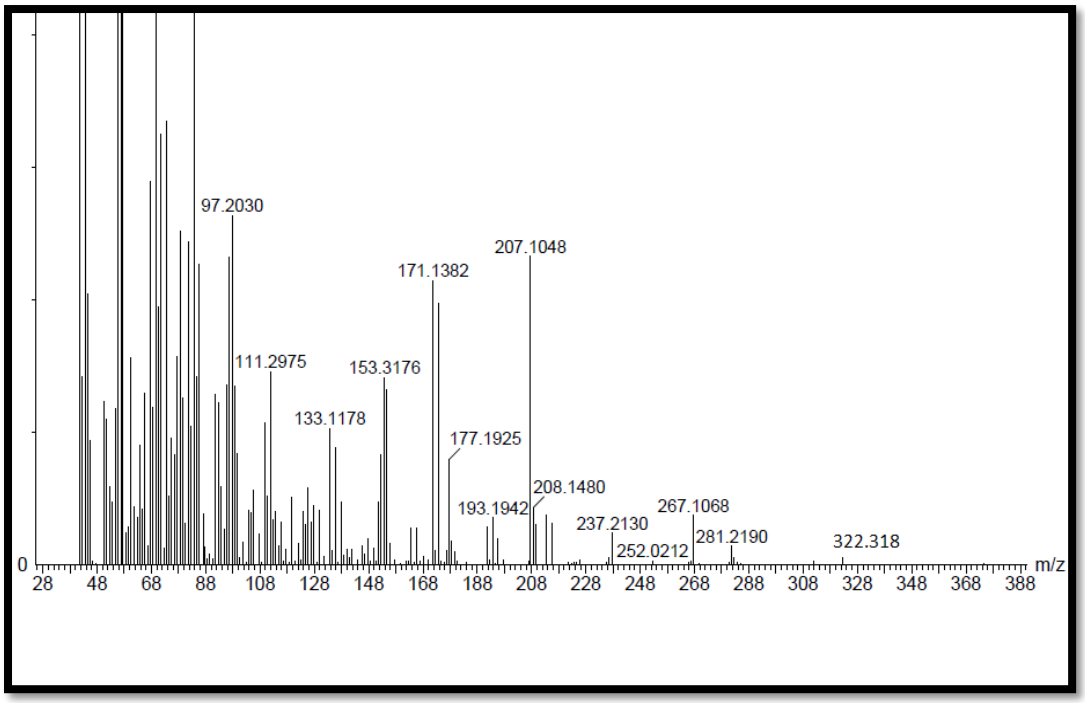
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3942.75	63.2331	2	3909	66.2596
3	3898.4	64.5089	4	3871.4	66.52
5	3862.72	66.0958	6	3853.08	65.7206
7	3836.68	59.6799	8	3823.19	67.3283
9	3791.37	70.8458	10	3769.19	68.3989
11	3746.05	67.6195	12	3736.4	66.6145
13	3720.98	67.8289	14	3661.19	41.6422
15	3645.77	28.2808	16	3634.2	28.6765
17	3614.91	25.1098	18	3606.23	21.4876
19	3585.02	17.381	20	3565.74	21.2422
21	3523.31	17.7744	22	3504.02	19.0002
23	3494.38	20.0432	24	3480.88	15.0673
25	3467.38	19.2723	26	3434.6	18.426
27	3424.96	19.3517	28	3406.64	18.723
29	3370.96	22.7154	30	3345.89	21.4228
31	3312.14	20.6813	32	3292.86	23.9957
33	3278.39	21.6069	34	3262	25.6888

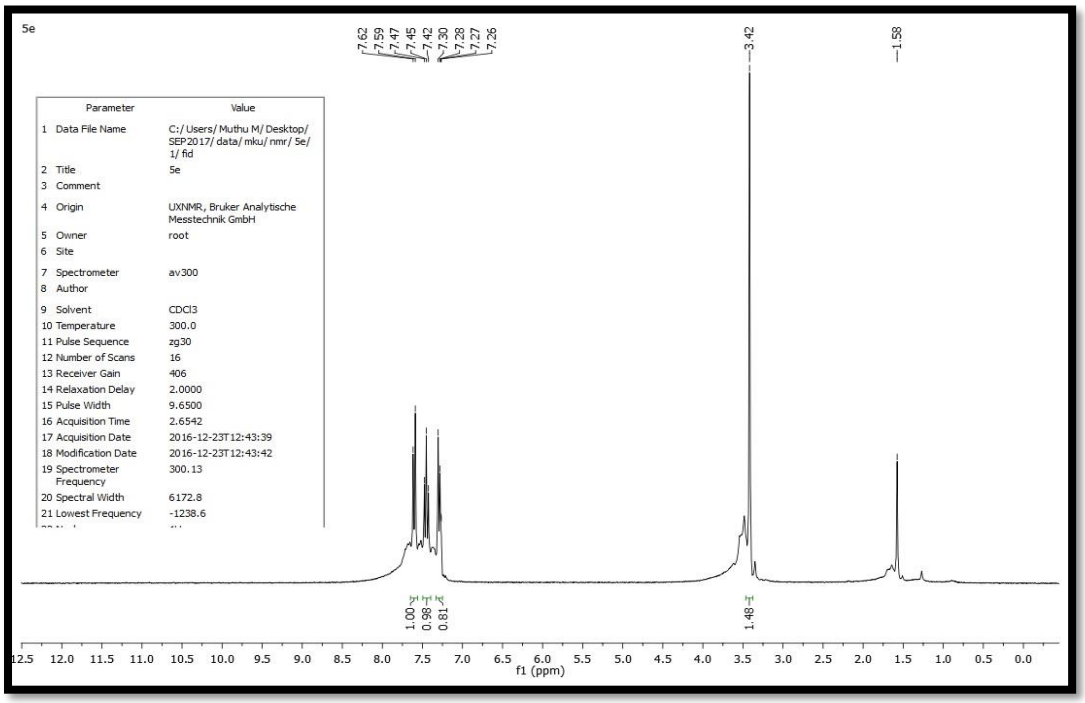
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
35	3220.54	30.4488	36	3192.58	30.0208
37	3055.66	41.0857	38	3021.91	49.728
39	2992.98	53.3215	40	2918.73	37.6076
41	2888.84	53.6986	42	2674.78	93.7802
43	2636.21	93.9102	44	2461.69	89.5128
45	2372.01	80.5383	46	2361.41	81.4982
47	2353.69	76.6786	48	2337.3	74.3562
49	2328.62	78.5516	50	2069.25	64.9392
51	1932.32	67.4111	52	1601.59	28.7552
53	1449.24	58.019	54	1421.28	54.1632
55	1384.64	45.1682	56	1367.28	43.2864
57	1193.72	41.1273	58	1120.44	25.0558
59	838.683	45.041	60	783.922	24.7908
61	746.317	32.6104	62	655.679	30.1724
63	601.682	22.0791	64	500.437	36.7553
65	447.404	36.2073	66	415.585	35.8389
67	404.978	36.0044			

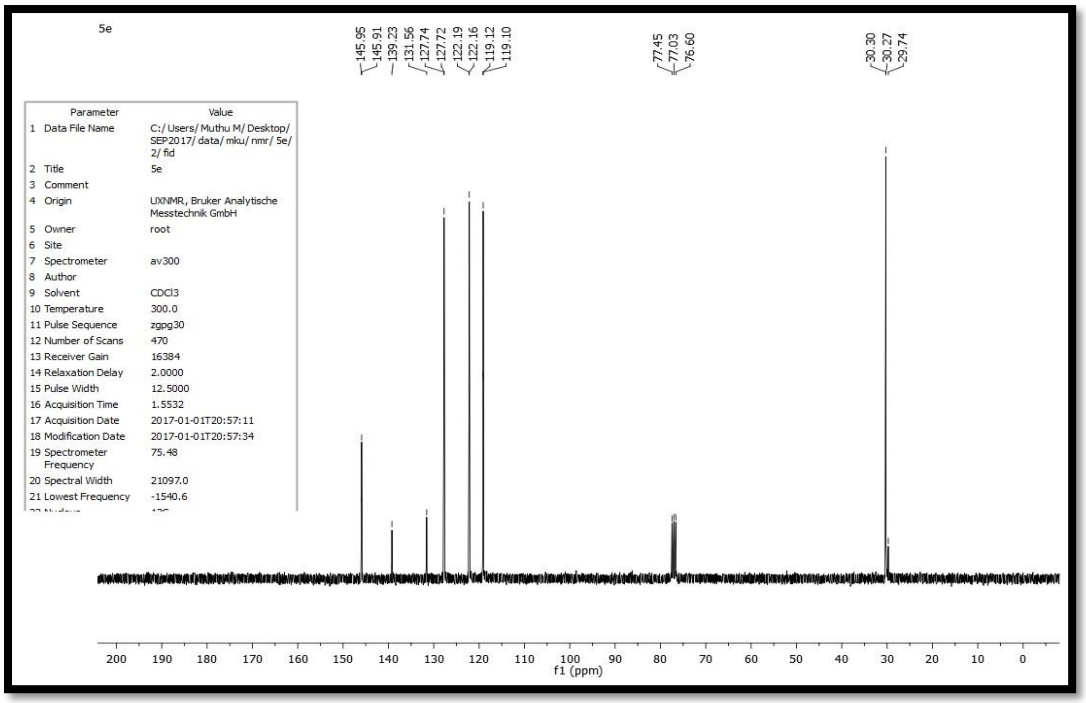
MASS SPECTRA



^{1}H NMR



^{13}C NMR


5e
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145.91
139.23
131.56
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119.12
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77.45
77.03
76.60
30.30
30.27
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Parameter
Value
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UXNMR, Bruker Analytische Messtechnik GmbH
5 Owner
root
6 Site
7 Spectrometer
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8 Author
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CDCl3
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11 Pulse Sequence
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14 Relaxation Delay
2.0000
15 Pulse Width
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16 Acquisition Time
1.5532
17 Acquisition Date
2017-01-01T20:57:11
18 Modification Date
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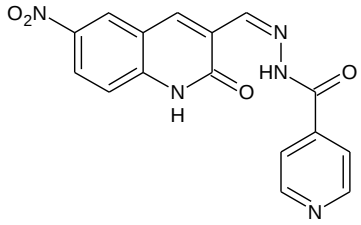
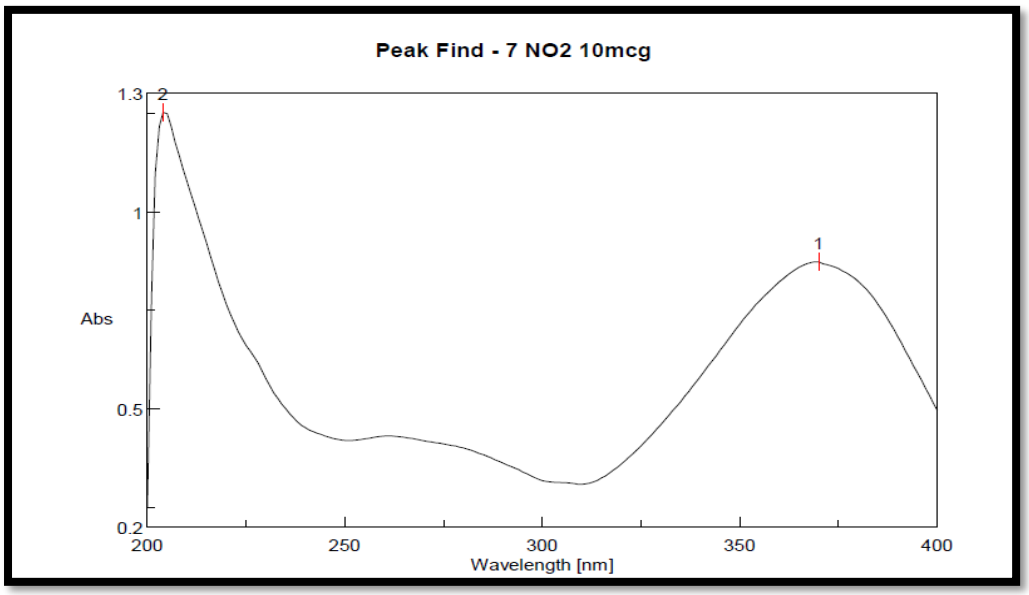
f1 (ppm)

Compound code-5f

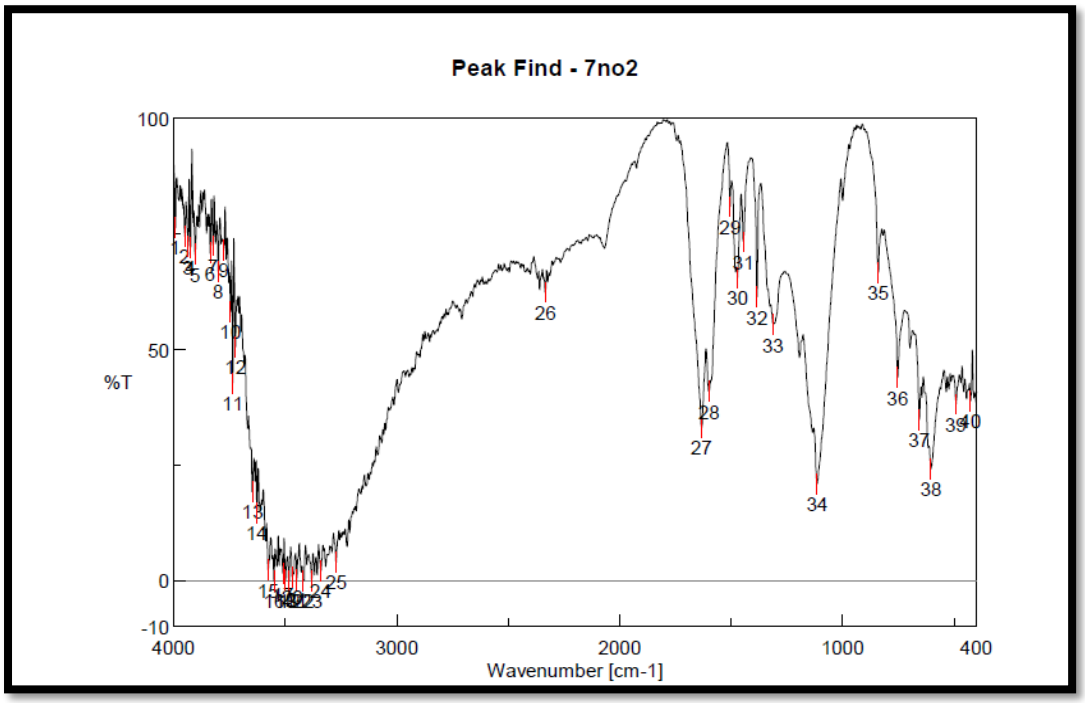


Chemical name	*N*'-[(7-nitro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :370nm
IR (KBr,v_{max} in cm^{-1})	C=0(ketone) -1632, C=O (amido)-1599 C=N -1505 N-N -1114 N-N=C -3340 N-O -1471 C=C (aromatic-1444



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	370	0.873202	2	204	1.25209



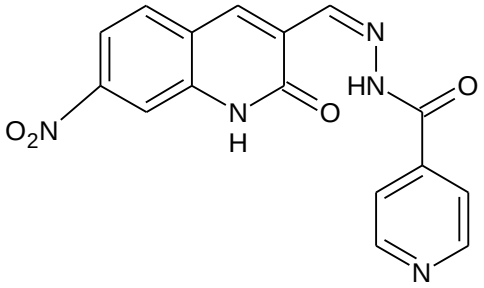
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3992.89	76.3239	2	3949.5	74.5172
3	3935.04	72.2445	4	3924.43	72.0879
5	3904.18	70.5218	6	3835.72	70.8415
7	3824.15	72.5095	8	3800.04	66.9213
9	3774.97	71.534	10	3745.08	58.0842
11	3735.44	42.6962	12	3722.91	50.5224
13	3646.73	19.1808	14	3626.48	14.4857
15	3576.34	2.23831	16	3550.31	-0.203077
17	3509.81	1.41803	18	3498.24	0.0071556
19	3482.81	-0.123406	20	3467.38	0.677395
21	3448.1	0.154582	22	3419.17	-0.0803274
23	3380.6	-0.128025	24	3340.1	2.02029
25	3271.64	3.88144	26	2333.45	62.3017
27	1632.45	33.0678	28	1599.66	40.9173
29	1505.17	80.9264	30	1471.42	65.5687
31	1444.42	73.2805	32	1384.64	61.3696
33	1311.36	55.3542	34	1114.65	20.8677

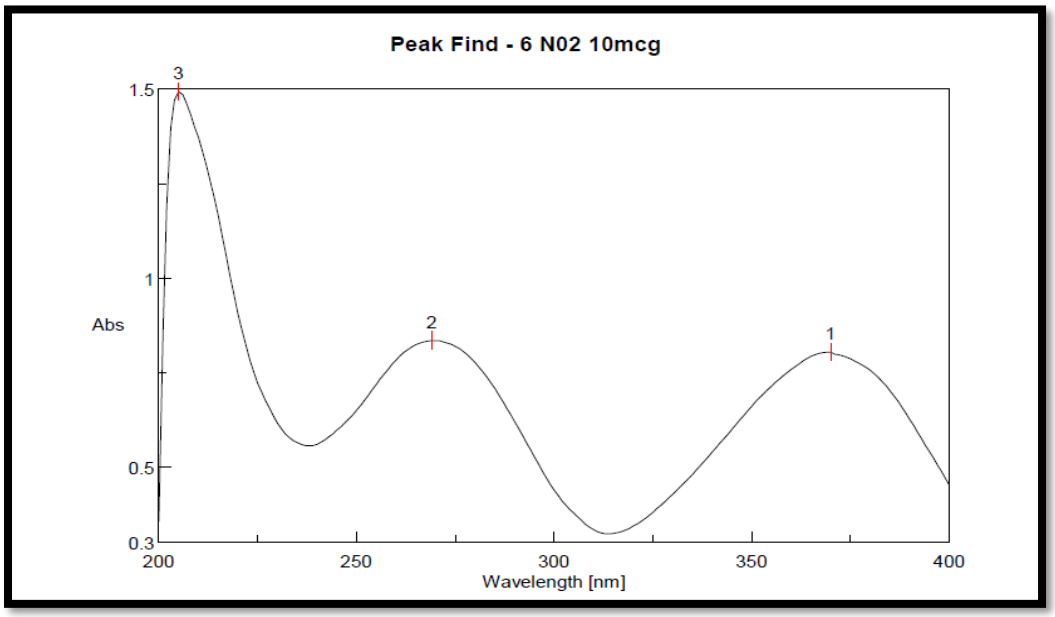
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
35	840.812	66.6037	36	753.066	43.8724
37	655.679	34.7225	38	603.61	24.1114
39	491.759	38.1276	40	426.191	38.8184

Compound code-5g



Chemical name	*N*'-[(6-nitro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :370nm
IR (KBr,v_{max} in cm^{-1})	C=0 (ketone) -1599, C=O (amido)-1632 C=N -1471 N-N -1114 N-N=C -3352 N-O -1471 C=C (aromatic)-1444



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
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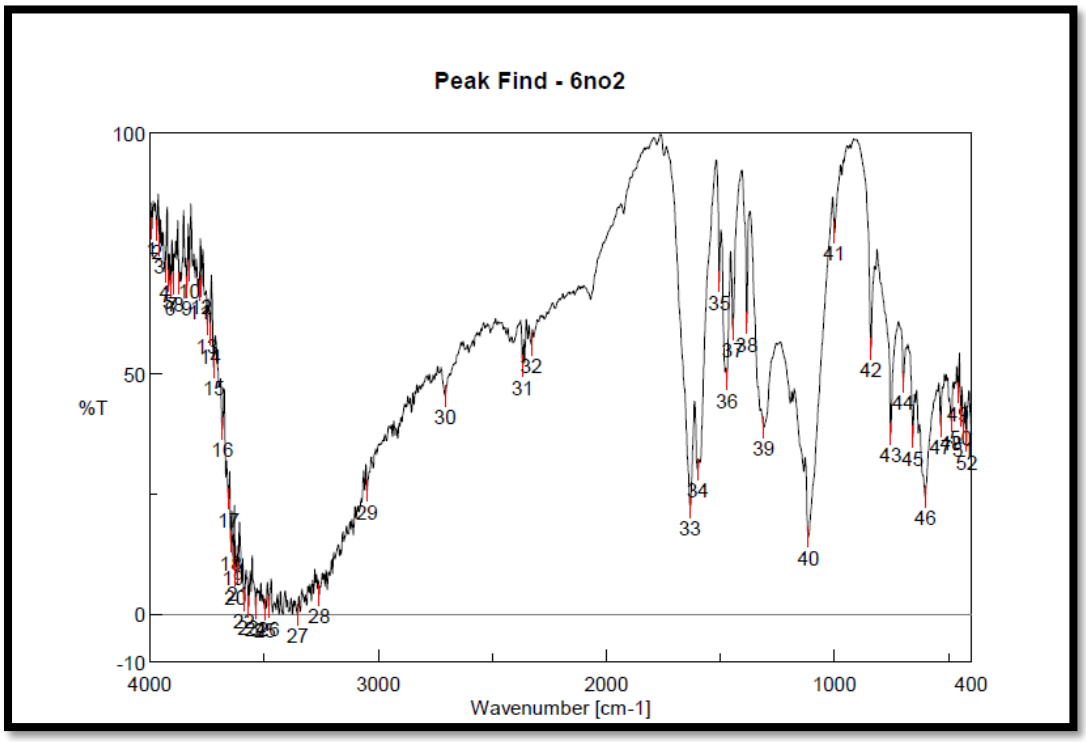
3	205	1.49324			



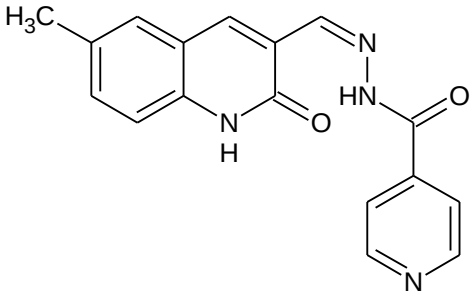
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3991.93	80.1476	2	3969.75	79.7313
3	3958.18	76.6292	4	3934.07	71.2383
5	3919.61	69.3752	6	3909.97	68.1229
7	3899.36	68.7902	8	3871.4	68.8842
9	3837.65	68.0181	10	3827.04	71.6015
11	3783.65	67.2826	12	3774.01	68.2149
13	3748.94	60.2439	14	3735.44	58.0008
15	3720.98	51.3147	16	3682.41	38.5683
17	3655.41	23.9977	18	3646.73	14.984
19	3636.12	11.7834	20	3624.55	7.94725
21	3613.95	8.59858	22	3587.91	2.94324
23	3567.66	1.45298	24	3535.84	1.24268
25	3497.27	0.982647	26	3478.95	1.38542
27	3352.64	-0.0845065	28	3258.14	4.02144
29	3048.91	25.7054	30	2706.6	45.4004
31	2366.23	51.5193	32	2329.59	56.0556
33	1632.45	22.2642	34	1599.66	30.0861

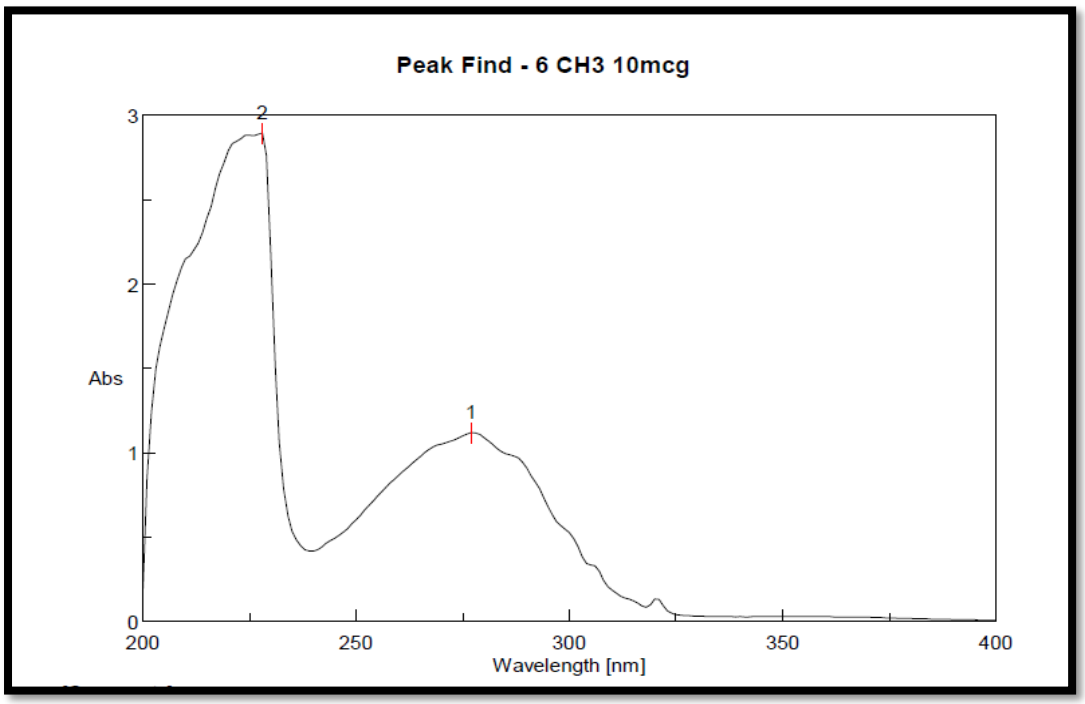
[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
35	1505.17	69.1076	36	1471.42	48.7345
37	1444.42	59.2096	38	1384.64	60.5533
39	1309.43	38.8305	40	1114.65	16.0173
41	999.91	79.355	42	839.847	55.2597
43	753.066	37.4648	44	698.105	48.3033
45	656.643	36.7588	46	602.646	24.4333
47	534.185	39.1066	48	487.902	40.1126
49	458.011	46.0237	50	446.44	41.1102
51	434.869	38.4899	52	421.37	35.9646

Compound code-5h



Chemical name	*N*'-[(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide
UV spectrum	Solvent used :METHANOL ʎ max :277nm
IR (KBr,v_{max} in cm^{-1})	C=0(ketone) -1602, C=O C=N -1382 N-N -1120 N-N=C -3426 C-CH_3 -2921 C=C(aromatic) -1384



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
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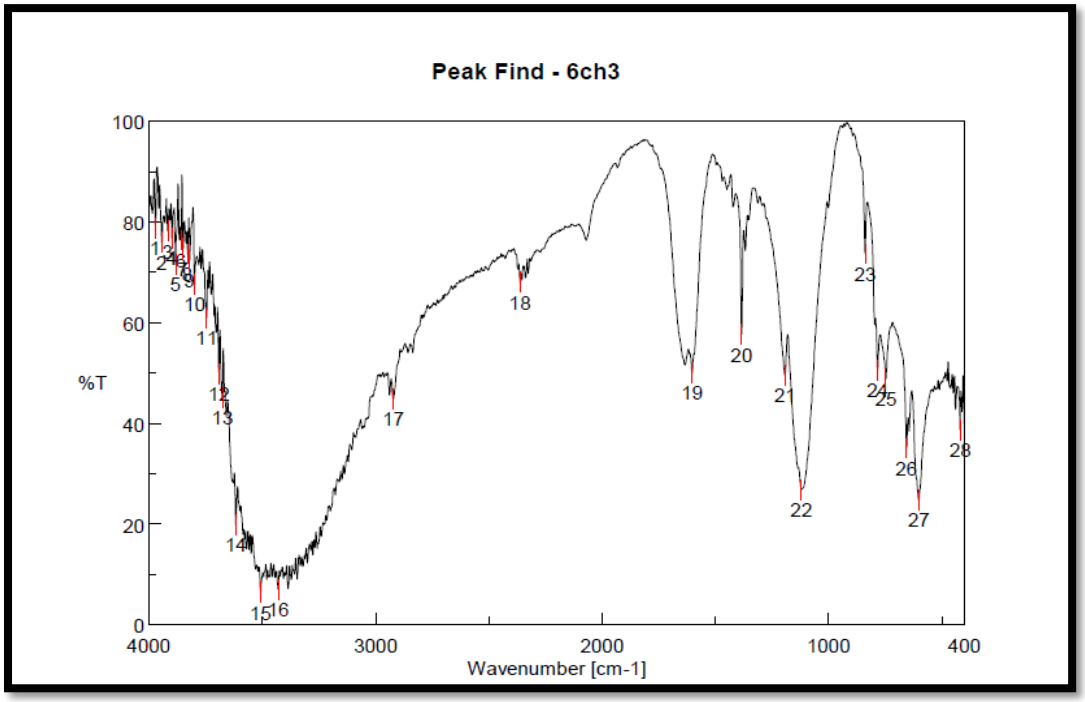


[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3971.68	78.9237	2	3942.75	75.9676
3	3916.72	78.2131	4	3898.4	76.8134
5	3882.97	71.5736	6	3859.83	76.4142
7	3849.22	74.8111	8	3828.97	73.6738
9	3820.29	72.3309	10	3799.08	67.6687
11	3746.05	61.0615	12	3691.09	49.7932
13	3676.62	45.1643	14	3616.84	19.8293
15	3506.92	6.36943	16	3429.78	6.99487
17	2921.63	44.8796	18	2361.41	68.0127
19	1602.56	50.0623	20	1384.64	57.681
21	1192.76	49.6686	22	1120.44	26.8039
23	838.883	73.7116	24	783.922	50.6344
25	747.281	48.906	26	655.679	35.0988
27	602.646	24.7726	28	419.442	38.6934

RESULT AND DISCUSSION

Antimycobacterial activity

All the newly synthesized compounds were screened for their antimycobacterial activity against *Mycobacterium tuberculosis* of H37RV Strain Using pyrazinamide 3.125 µg/ml,streptomycin 6.125 µg/ml and ciprofloxacin 3.125µg/ml as standards.

Three of the newly synthesized compounds 5d,5e,5h were resistant and showed no activity ,where five of the newly synthesized compounds 5a,5b,5c,5f,5g showed potent antimycobacterial activity by inhibiting the growth at concentration of 6.25µg/ml **.**Compound 5c exhibited the highest activity by inhibiting the growth at concentration 3.125µg/ml.

Antibacterial activity

All the newly synthesized compounds were screened for their antibacterial activity against both Gram positive and Gram negative organisms using Ofloxacin (500µ/ml) as the standard.

The newly synthesized compound 5a,5c,5d,5e,5f,5g,5h were resistant and compound 5c was moderately sensitive against the test microorganism Staphylococcus aureus NCIM 2079 at 500µg/ml concentration. The compound 5c exhibited the highest activity.

The compounds 5a,5d,5e,5h were resistant and compound 5b was moderately sensitive and compounds 5c,5f,5g were sensitive against the test microorganism Bacillus subtilis NCIM 2063 at 500µg/ml concentration. The compound 5c exhibited the highest activity.

The compounds 5a,5b,5d,5e,5h were resistant and compounds 5c,5f,5g were sensitive against the test microorganism *Pseudomonas aeruginosa* NCIM 2036 at 500µg/ml concentration. The compound 5c exhibited the highest activity.

The compounds 5a,5d,5e were resistant and compound 5h was moderately sensitive and compounds 5c,5f,5g were sensitive against the test microorganism Escherichia coli NCIM 2918 at 500µg/ml concentration. The compound 5c,5f exhibited the highest activity.

Antifungal activity

All the newly synthesized compounds were screened for their antifungal activity against *Candida albicans* NCIM 3100 and *Aspergilus niger* NCIM 596 by agar disc diffusion method using Flucanazole 10µg/disc as the standard. 10µg/disc was used for all the test compounds.

The compounds 5a,5d,5e,5h were resistant and compounds 5b,5c,5f,5g were sensitive against the test microorganism Candida albicans NCIM 3100 at 100µg/disc concentration. The compound 5c exhibited the highest activity

he compounds 5a,5b,5d,5e,5h were resistant compounds 5c,5f,5g were moderately sensitive against the test microorganism *Aspergilus niger* NCIM 596 at 100µg/disc concentration. The compound 5c,5f exhibited the highest activity.

SUMMARY AND CONCLUSION

With the view of synthesizing new compounds with minimum side effects, less toxicity, non-resistant and more selective against disease-producing microorganisms, the present work was undertaken to synthesize 8 different Schiff bases of 3-formyl-2-quinolone and substitutes of 3-formyl-2-quinolones with isoniazid.

LITERATURE REVIEW

The extensive literature reports showed that the Schiff bases of 3-formyl-2- quinolones are potent antimicrobial agents. The 2-Quinolone moiety and Schiff bases posses excellent antimicrobial activity.

SCHEME

All the intermediate and final compounds are synthesized by traditional method.

STEP 1:

Initially Acetanilde and substituted acetanilides were prepared by refluxing aniline and substituted anilies with acetic acid and zinc dust**.**

STEP 2:

2-chloro-3-formyl quinoline and substituted 2-chloro-3-formyl quinolines were synthesized from acetanilide and substituted acetanilides correspondingly using Vilsmeier Haack reaction**.**

STEP3:

The synthesized compounds were refluxed with a 70% acetic acid to give 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones

STEP4:

Finally, 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones were refluxed with isoniazid in presence of ethanol and concentrated sulphuric acid to get different Schiff bases.

SPECTRAL STUDIES

Structures of all the newly synthesized compounds were confired by UV,IR, MASS and NMR.

A) Antimycobacterial activity

Antitubercular screening of the synthesized compounds were done by Alamar Blue assay method in Middlebrook 7H9 broth against *Mycobacterium tuberculosis* H37RV strain (ATCC No. 27294). Four of newly synthesized compounds **5a,5b,5f,5g** showed antimycobacterial activity by inhibiting the growth at concentration of 6.25µg/ml ,where compound **5c** inhibited the growth at concentration of 3.125µg/ml .other three newly synthesized compounds were resistant and showed no activity.

B) Antibacterial screening

The synthesized compounds were screened for antibacterial activity against both gram positive (*Staphylococcus aureus* NCIM 2079 and *Bacillus subtilis* NCIM 2063) and gram negative (*Escherichia coli* NCIM 2911 and *Pseudomonas aeruginosa* NCIM 2036) organisms by Kirby-Bauer method. Three of eight compounds were found to be sensitive active against bacteria. **5c,5f,5g** were found to be sensitive activity against Gram positive bacteria and Gram negative bacteria.

C) Antifungal screening

All the newly synthesized compounds were screened for antifungal activity *Candida albicans* NCIM 3100 and *Aspergillus niger* NCIM 596 by agar diffusion method using Flucanazole(10µg/disc) as the standard. 100µg/disc was used for all the test compounds.

The compounds 5b, 5c, 5f, 5g exhibited the highest activity towards *Candida albicans.*

CONCLUSION

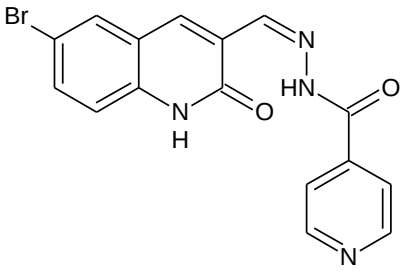
Based on the results of synthetic works, characterization data, antimicrobial screening and antimycobacterial screening the following conclusions were made.

- Using the schemes evolved, eight different Schiff bases of 3-formyl-2-quinolone and substituted 3-formyl-2-quinolones were synthesized in good yields.
- Four synthesized derivatives (5a,5b,5f,5g) showed equipotent antitubercular activity compared to the standard streptomycin at concentration of 6.12µg/ml. Compound 5c showed equipotent antitubercular activity compared to the standards Pyrazinamide and Ciprofloxacin at concentration of 3.125µg/ml
- The synthesized compounds showed poor to moderate antibacterial activity.

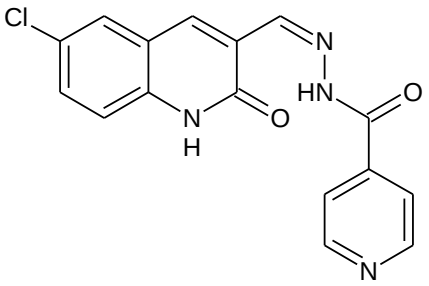
The *in vitro* antimicrobial studies showed that three of eight compounds exhibited good antibacterial activity in which compound 5c showed the highest activity against *Bacillus subtillis* NCIM 2063 and *Pseudomonas aeruginosa* NCIM 2036. The compounds 5b,5c,5f,5g exhibited the highest antifungal activities.

- Among the synthesized compounds 5b,5c,5f,5g can be taken as the lead molecule and acute toxicity studies are to be done on these promising compounds.

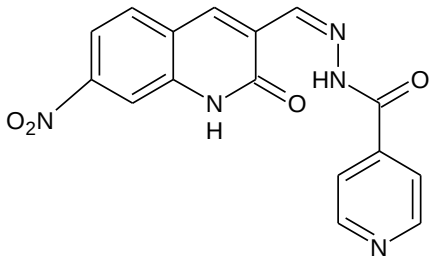
5b



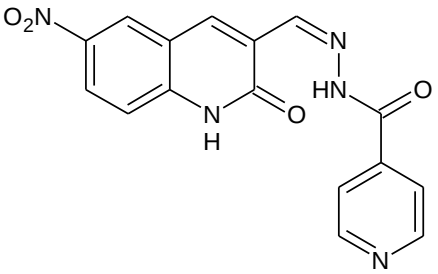
5c



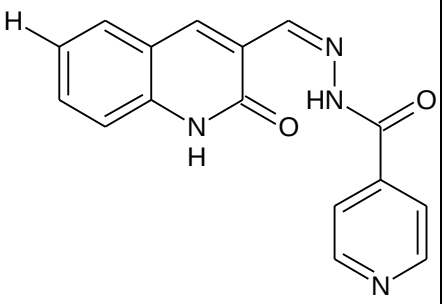
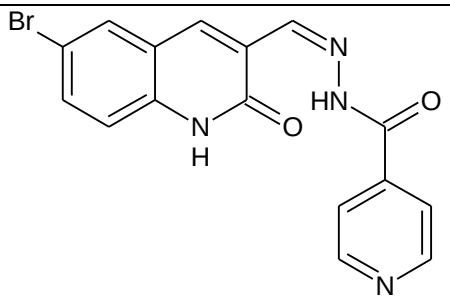
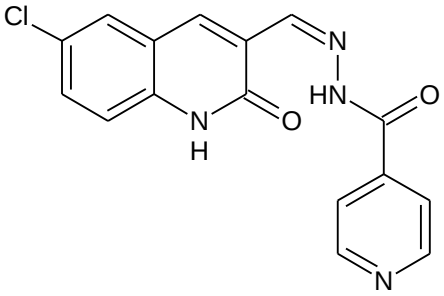
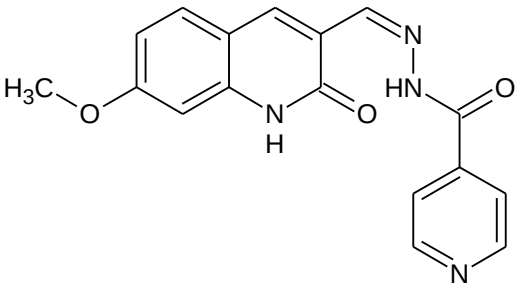
5f

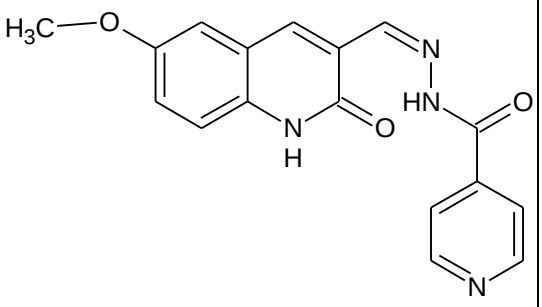
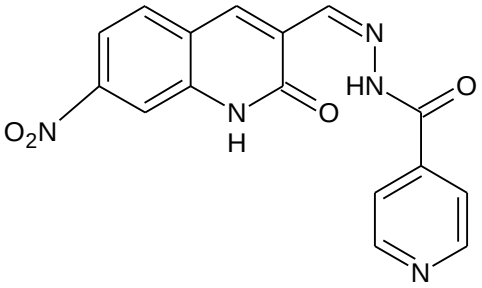
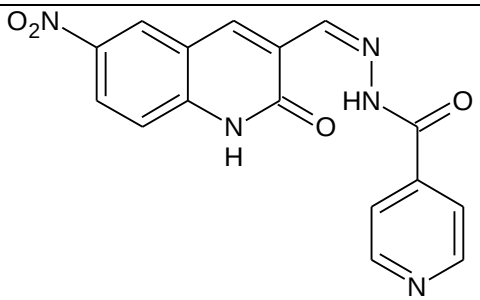
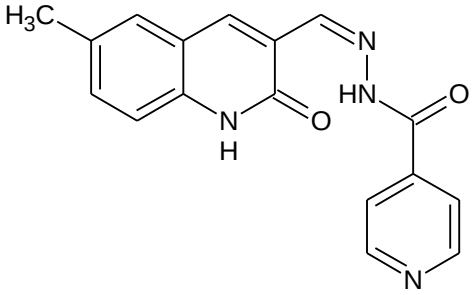


5g



LIST OF NEWLY SYNTHESIED DRUGS

COMPOUND CODE	IUPAC NAME	STRUCTURE
5a	*N*'-[(2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5b	*N*'-[(6-bromo-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5c	*N*'-[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5d	*N*'-[(7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	

5e	*N*'-[(8-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5f	*N*'-[(7-nitro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5g	*N*'-[(6-nitro-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	
5h	*N*'-[(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylidene]pyridine-4-carbohydrazide	

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